ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL

Vol. 11, Number 1 **February 1959**

THE RELATIONSHIP OF EPILEPSY TO BREECH DELIVERY [1]

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(Received for publication: April 15, 1958)

INTRODUCTION

From antiquity epilepsy has been known to result from cranial injury; and the association of convulsive seizures with numerous cerebral diseases has been amply described (Penfield and Jasper 1954). Still, in the majority of patients with epilepsy, cerebral lesions cannot be demonstrated even with the aid of modern diagnostic methods. Patients lacking evidence of cerebral damage are said to have idiopathic epilepsy, the disease thought to result from intrinsic instabilities of cerebral function established through the operation of hereditary factors (Lennox 1935, 1951; Lennox *et al.* 1939, 1940). On the basis of clinical and EEG manifestations, patients with epilepsy can be segregated into two prominent groups (Gibbs *et al.* 1943; Jasper and Kershman 1941, 1949).

1. Patients with focal cerebral seizures with localized paroxysmal EEG abnormalities (FCS).

2. Patients with non-focal cerebral seizures with diffusely distributed, bilaterally synchronized spike and wave EEG discharges (SSW).

Patients with focal cerebral seizures experience sensory, motor or psychical aurae of impending attacks. Some lose consciousness and behave in an inappropriately automatic fashion (psychomotor seizures). EEG's in these cases often reveal localized paroxysmal discharges; and Penfield (1954) has observed atrophic — and other — lesions in electrically abnormal zones of cortex in a large proportion of his cases at operation. Patients with non-focal seizures (SSW) rarely have warnings of attacks, their seizures commencing with abrupt loss of consciousness; they have petit mal, myoclonic, akinetic, or grand mal seizures. EEG's in such cases often reveal bilaterally synchronous high voltage (300 μV.) spike and wave discharges. Frequently the spike and wave components of these discharges are strikingly uniform occurring at a regular 3 per sec. rate; but variations in the form and rate of the spike and waves are common (Gibbs and Gibbs 1952). Cases with SSW, lacking neurological signs or evidences of progressive deterioration, are rarely found to have cerebral lesions. These cases constitute

[1] This study was supported in part by the Greater Detroit Council for Epilepsy.

the major portion of the epileptic population thought to have what is called idiopathic, essential, cryptogenic, genetic, or centrencephalic epilepsy.

The interrelationship of petit mal to myoclonic, generalized, and brief tonic seizures occurring in patients with EEG's showing the diffuse spike and wave reaction is not clearly understood. Likewise there are believed to be fundamental differences between the well regulated 3 per sec. spike and slow waves occurring in long trains, and other similar but more irregular and interrupted paroxysmal rhythms (Clark and Knott 1955). Patients with EEG's showing imperfectly symmetrical 2 per sec. spike and wave discharges are said to have "petit mal variant" and are thought to have brain damage (Lennox 1959; Lennox and Davis 1950).

The present report is based upon an investigation wherein the symptoms and signs of children afflicted with neurologic disorders were correlated with gestational and parturitional factors known to be associated with high rates of infant mortality. The object of the study was to determine whether any one factor was more strongly associated with one type of neurologic disorder than another. This article deals with the relationship of breech delivery to epilepsy; particular attention being given to "idiopathic" (SSW) epilepsy.

CLINICAL MATERIAL AND COLLECTION OF THE DATA

The presence or absence of neurologic symptoms and signs was recorded in an inclusive manner for all cases of epilepsy, cerebral palsy, and mental deficiency examined by the author; a few had other conditions. There was a total of 706 patients ranging in age from 2 to 30 years. All but a few came from homes in the region of Detroit and were from families with good standards of nutrition and health. Neurologic findings and descriptions of seizures — if any — were recorded; and the cases were classified on the basis of these manifestations into: 1, a group with epilepsy, and 2, a group without epilepsy (table I).

The group with epilepsy was divided into the following subgroups on the basis of EEG findings: those with (1) diffusely distributed bilaterally synchronized high amplitude spike and wave discharges (SSW); (2) localized spike discharges or asymmetrical abnormally irregular activities (FCS); (3) diffusely hypersynchronous or abortive, larval spike and wave activities (diffuse dysrhythmia); (4) diffuse paroxysmal activity in cases with abnormal neurologic signs (obvious diffuse brain damage); (5) negative EEG's; (6) no EEG's obtained.

TABLE I

Incidence of Breech Delivery Surviving Neonatal Period

Source	*Seeley*	*Guyer and Heaton*	*Henry Ford Hospital*	*Total*
Births	25,532	15,398	2,411	43,341
Breech	945	488	74	1,507
Per Cent Breech	3.701	3.169	3.069	3.477

The tracings in each case were interpreted and assigned to one of the subgroups listed above after all identifying notations had been hidden from view. Much of the data had been obtained before the relationship of any factor of birth to any particular neurologic disorder was suspected. The suspicion of a significant relationship between breech delivery and epilepsy emerged from a preliminary inspection of the data; subsequently, therefore, all cases presenting the complaint of recurrent convulsions were assigned to one of the categories on the basis of clinical and EEG findings before the history of birth was obtained.

Data regarding the general factors of gestation and delivery were obtained from the parents or hospital records. The information about the mode of presentation, with which this study is particularly concerned, is believed to be reasonably accurate. In the few instances where information of the mode of birth was not available, the assumption was made that these patients were born by vertex presentations. It will be seen that this as-

sumption weights the analysis against the positive correlations obtained. Other than a routine hyperventilation test, no activation procedures were used.

The incidence of breech born individuals (surviving the neonatal period) in the general population was determined to be 3.447 per cent by combining series of Seeley (1949), Guyer and Heaton (1945) and of our own at Henry Ford Hospital (table II). This value is close to that found by Hall and Kohl (1956), their incidence being 3.0 per cent.

TABLE II

Case Grouping

	Cases	*Breech*	*Per cent Breech*	*Breech Twins*
Group 1 — No epilepsy	390	29	7.44	4
Group 2 — Epilepsy	265	39	14.72	6
Subgroup 1 — SSW	92	18	19.57	4
Subgroup 2 — FCS	71	2	2.82	0
Subgroup 3 — Diffuse dysrhythmia	17	6	35.29	1
Subgroup 4 — Complex diplegia	22	3	13.64	0
Subgroup 5 — Negative EEG	50	9	18.00	1
Subgroup 6 — No EEG	13	3	23.08	0

ANALYSIS OF THE DATA

From a total of 706 patients seen by the author, 51 were deducted because the histories of birth were wholly inadequate, the parents being unavailable, the child being an orphan, or hospital records being unobtainable. The 51 excluded cases were found to be fairly evenly distributed among the groups and subgroups: there being 35 in the non-epilepsy group, 16 in the epilepsy group, 7 in the SSW subgroup, 4 in the FCS subgroup, and 5 in the remaining subgroups. There were for analysis 655 patients of whom 265 had epilepsy and 390 had no epilepsy. In the group of 265 patients with epilepsy, 39 were breech born (14.72 per cent); while in the group of 390 patients with no epilepsy, 29 were breech born (7.44 per cent). Comparison of the two groups revealed a distinctly significant difference.[1]

Further statistical analysis was confined to the SSW and FCS subgroups; no further analysis was carried out with the other subgroups. Cases in the third subgroup (diffuse dysrhythmia) could not be classified with either the SSW or FCS subgroups; but the author believed that the epileptic disorders in most of the cases in this subgroup were closely allied to those in the SSW subgroup, and were not akin to those in the FCS subgroup. Six of the 17 patients (35.3 per cent) in the diffuse dysrhythmia subgroup were breech born.

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[1] All statistical comparisons were made by means of the Chi square test. Probabilities (P) greater than 0.01 were considered not significant; less than 0.01 but greater than 0.001 were considered suggestively to probably significant; less than 0.001 definitely to very significant. Comparison of the epilepsy to the no epilepsy groups in respect to breech delivery reveals $X^2 = 9.0$, $V = 1$ and, $P = 3.2 \times 10^{-3}$.

There were 92 SSW cases of which 18 were breech born (19.57 per cent) (table II). Comparison of this subgroup to the group with no epilepsy revealed that breech birth occurred much more often than could be expected by chance.[1] In sharp contrast, comparison of the 71 FCS cases, of which 2 were breech born, to the group with no epilepsy revealed no significant difference in regard to breech birth.[2] Comparison of the SSW subgroup to the general population in respect to the incidence of breech delivery revealed

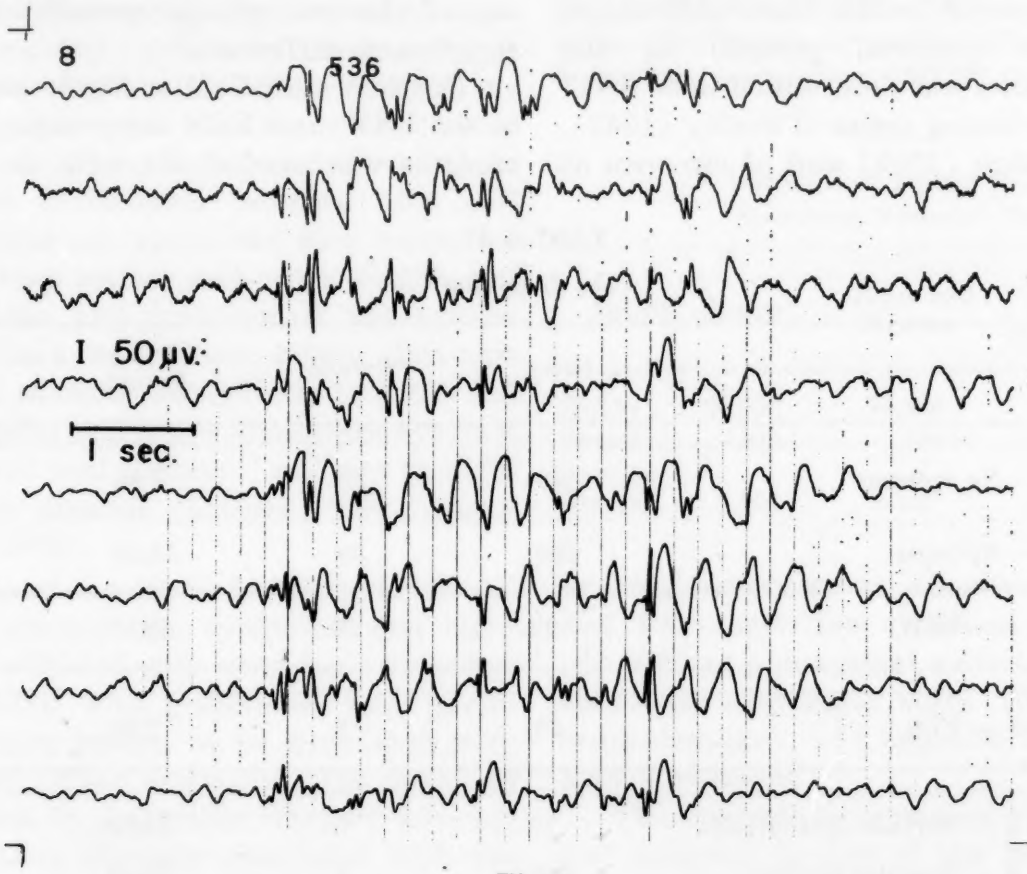

Fig. 1

EEG of child with observed petit mal attacks. Onset age 9. Electrode arrangement B. (see below).
Figures represent samples of EEG tracings obtained from breech born individuals who had non-focal epilepsy of the type associated with diffusely distributed, bilaterally synchronous spike and wave reactions. The EEG's figured were picked at random from the breech born group.
Case number in upper left corner. Amplitude is indicated by vertical bar; time by horizontal bar.

Electrodes are arranged either as A:

Channel 1.	(top)	L. Frontal to L. Ear	5. R. Frontal to R. Ear
2.		L. Central to L. Ear	6. R. Central to R. Ear
3.		L. Parietal to L. Ear	7. R. Parietal to R. Ear
4.		L. Occipital to L. Ear	8. R. Occipital to R. Ear

or as B:

Channel 1.	(top)	L. Frontal to L. Central	5. R. Frontal to R. Central
2.		L. Central to L. Temporal	6. R. Central to R. Temporal
3.		L. Temporal to L. Parietal	7. R. Temporal to R. Parietal
4.		L. Parietal to L. Occipital	8. R. Parietal to R. Occipital

[1] Comparison of the SSW subgroup to the no epilepsy group in respect to breech delivery reveals $X^2 = 12.5$, $V = 1$, and $P = 4.0 \times 10^{-4}$.

[2] Comparison of the FCS subgroup to the no epilepsy group in respect to breech delivery reveals $X^2 = 2.0$, $V = 1$, and $P = 0.15$.

a very significant difference,[1] while, on the other hand, no significant difference was found upon comparing the FCS subgroup to the general population.[2] Comparison of the SSW to the FCS subgroup in regard to breech delivery revealed a significant difference, breech delivery being much more frequent in the SSW subgroup.[3]

The author has recently found a positive correlation between epilepsy and twinning (to be published). Therefore, the comparisons made above were repeated after deducting breech born twins from the groups and subgroups. The results of comparisons corrected for breech born twins were not significantly altered, indicating that the significant differences found were not contingent upon the presence of twins among the breech born.[3-9]

Among the breech born cases with SSW a familial history of epilepsy was known in 2 cases and denied in 14, relatives being inadequately known in the other 2 cases. Four of the cases (table III - cases 1, 7, 8, 15; fig. 2, 5) were one of twins; the sibling of one also had epilepsy, and the sibling of two

TABLE III

Clinical Features of Breech Born SSW ("Idiopathic Epilepsy") Cases

Case	*Age of Onset*	*Seizure Type*	*Age of Walking in Months*	*Mentality*
1	2/12	Myoclonic	14	dull
2	9	Petit Mal	14	B student
3	13	Petit Mal	24	D student
4	5/12	Myoclonic	14	dull
5	5	Grand Mal	14	C student
6	13	Petit Mal	36	D student
7	1	Grand Mal	12	normal
8	2	Petit Mal + Myoclonic	14	I.Q. 77
9	9	Petit Mal	10	A student
10	7	Petit Mal + Grand Mal	12	C student
11	6	Petit Mal + Myoclonic	17	E student
12	8	Petit Mal	10	B student
13	30	Petit Mal + Grand Mal	12	C student
14	4/12	Petit Mal + Grand Mal	16	dull
15	7	Petit Mal + Grand Mal	10	B student
16	9	Petit Mal + Grand Mal	30	E student
26	7	Myoclonic	11	I.Q. 101
27	5	Petit Mal	12	C student

1 Comparison of the SSW subgroup to the general population in respect to breech delivery reveals $X^2 = 70.9$, $V = 1$, and $P = 3.8 \times 10^{-17}$.

2 Comparison of the FCS subgroup to the general population in respect to breech delivery reveals $X^2 = 0.1$, $V = 1$, and $P = 0.75$.

3 Comparison of the SSW subgroup to the FCS subgroup in respect to breech delivery reveals $X^2 = 10.4$, $V = 1$, and $P = 1.2 \times 10^{-3}$.

4 Comparison of the epilepsy group to the no epilepsy group in respect to breech delivery, breech born twins having been deducted reveals $X^2 = 8.2$, $V = 1$, and $P = 3.7 \times 10^{-3}$.

5 Comparison of the SSW subgroup to the no epilepsy group in respect to breech delivery, breech born twins having been deducted, reveals $X^2 = 10.4$, $V = 1$, and $P = 1.2 \times 10^{-3}$.

6 Comparison of the FCS subgroup to the no epilepsy group in respect to breech delivery, breech born twins having been deducted, reveals $X^2 = 1.4$, $V = 1$, and $P = 0.23$.

7 Comparison of the SSW subgroup to the general population in respect to breech delivery, breech born twins having been deducted, reveals $X^2 = 40.5$, $V = 1$, $P = 1.9 \times 10^{-10}$.

8 Comparison of the FCS subgroup to the general population in respect to breech delivery, breech born twins having been deducted, reveals $X^2 = 0.1$, $V = 1$, and $P = 0.76$.

9 Comparison of the SSW subgroup to the FCS subgroup in respect to breech delivery, breech born twins having been deducted, reveals $X^2 = 8.4$, $V = 1$, and $P = 3.6 \times 10^{-3}$.

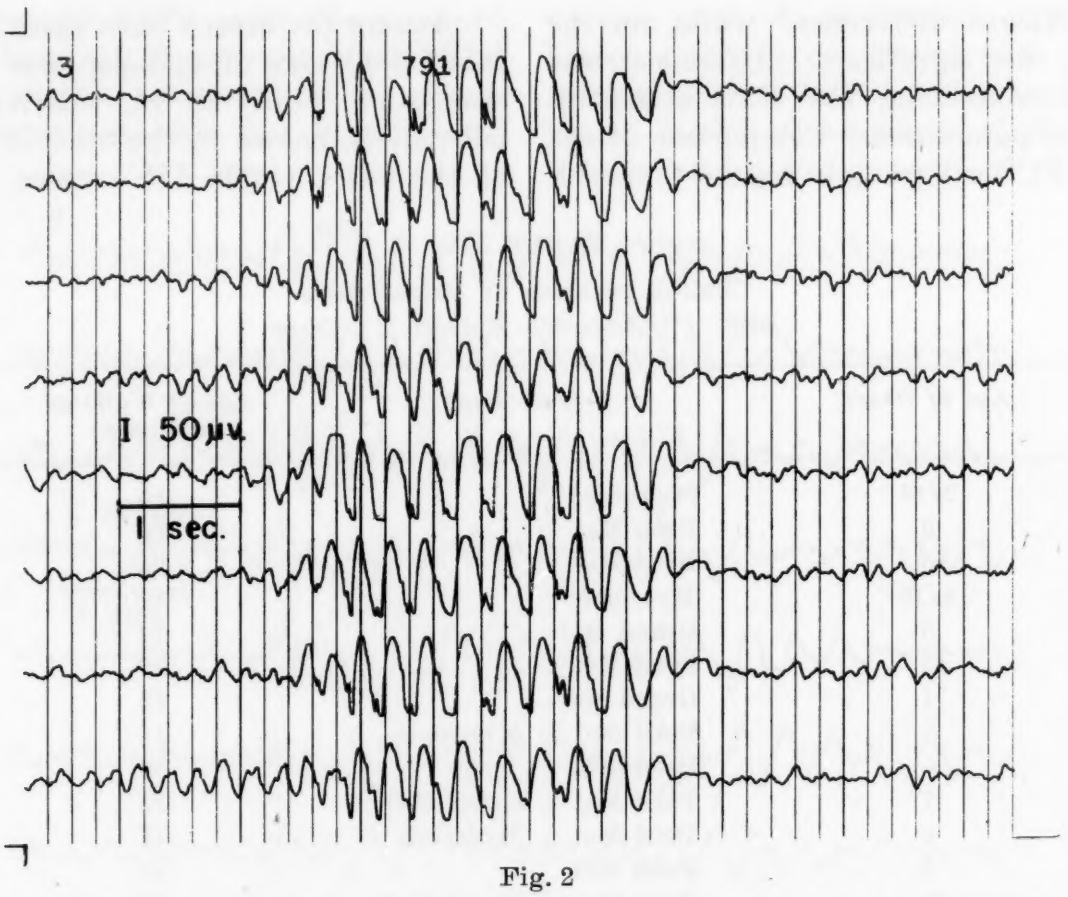

Fig. 2

EEG of breech born twin with both petit mal and myoclonic seizures beginning at age 2. Electrode arrangement B.

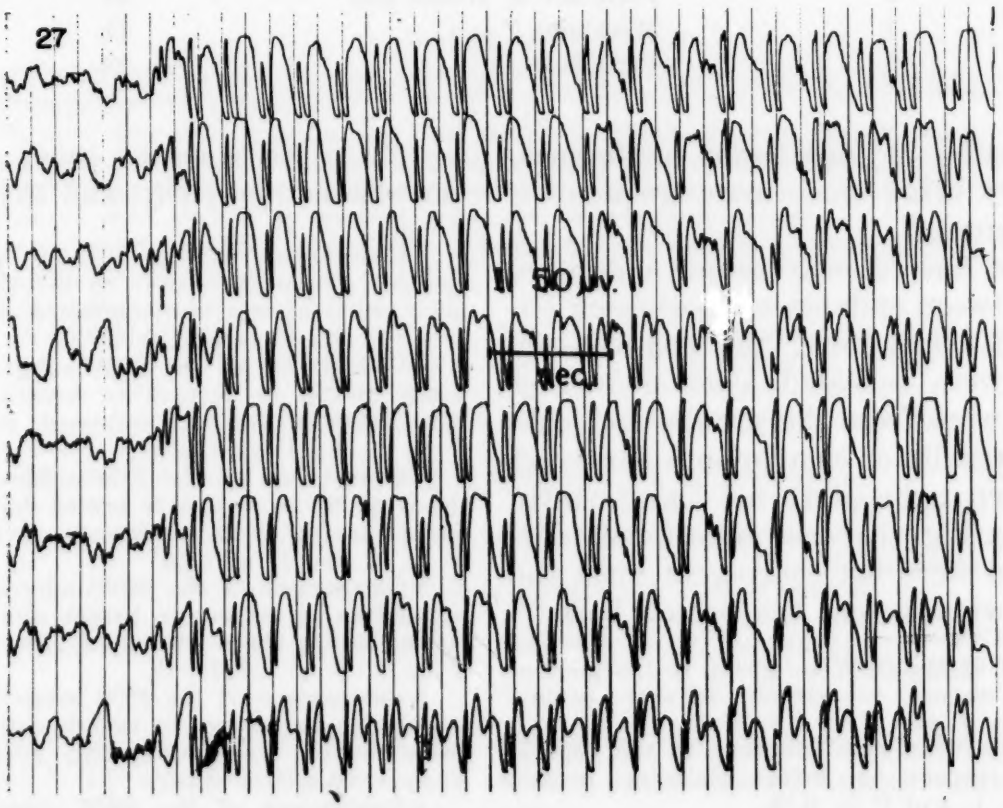

Fig. 3

EEG of boy with observed petit mal attacks. He had delayed onset of walking and was a poor student. Electrode arrangement A.

of the others died at birth. The duration of labor was over 20 hours in one case (table III - case 6; fig. 6); two cases (table III - cases 2, 8; fig. 1, 2) required artificial respiration at birth; only one (table III - case 8) weighed less than 5 lb. at birth. Neither prolapse of the cord nor intrapartum infection were known to have occurred in any case. No prenatal factors appeared to be of significance.

The mean age of onset of seizures of the breech born patients was 7.3 years, the range being between 2 months and 30 years; but the mean age of onset of the breech born patients with petit mal attacks was 9.2 years, the range being between 5 and 13 years. The mean age of onset of walking was 15.7 months in the breech born of the SSW subgroup, and even later (18.5 months) for those with petit mal attacks. Three patients experienced severe difficulty in learning, and three others probably will require special tutoring upon reaching school age.

It is not within the scope of the present report to describe the historical and clinical features of the entire subgroup of 92 SSW cases, but it might be pointed out that the characteristics of the breech born cases were fairly representative of the entire subgroup.

The subgroup of 92 SSW cases was subdivided according to the type of seizures experienced by the patients (table IV). There were 20 patients with petit mal or petit mal and grand mal seizures of which 8 were breech born (table III - cases 2, 3, 6, 9, 10, 12, 16, 27; fig. 1, 3, 4, 6). Comparison of the petit mal subdivision of the SSW subgroup to the group of cases without epilepsy and also to the general population regarding the occurrence of breech delivery revealed significant differences, the number of breech born in the petit mal subdivision being greater than can be expected by chance.[1, 2] There were 10 cases with myoclonic, in addition to petit mal, seizures; and there were 62 cases with myoclonic, grand mal, or other types of seizures, but without petit mal attacks. Comparison of the petit mal subdivision to the subdivision of cases with myoclonic and other types of seizures in regard to breech delivery, revealed that within the SSW subgroup there was a suggestively significant difference, breech delivery being more frequently associated with petit mal than other types of seizures.[3]

TABLE IV

Subdivision of the SSW (''Idiopathic Epilepsy'') Subgroup according to Seizure Type

Type of Seizure	*Type of Delivery*		*Total*	*Per cent Breech*
	Breech	*Other*		
Petit Mal only	6	12	18	33.3
Petit Mal + Grand Mal	2	0	2	100.0
Petit Mal + Myoclonic	3	7	10	30.0
Myoclonic, Grand Mal, and other	7	55	62	11.3

In the subgroup of 92 SSW cases there were 20 with ''classical spike and wave'' EEG abnormalities. The EEG's of these cases revealed trains of uniformly regular 2½ to 3½ per sec. spike and wave formations, the background patterns being normal in appearance. Of the 20 patients with the ''classical spike and wave'' 6 were breech born indi-

[1] Comparison of the petit mal subdivision of the SSW subgroup to the no epilepsy group in respect to breech delivery reveals $X^2 = 24.6$, $V = 1$, and $P = 7.2 \times 10^{-7}$.

[2] Comparison of the petit mal subdivision of the SSW subgroup to the general population in respect to breech delivery reveals $X^2 = 79.5$, $V = 1$, and $P = 5.1 \times 10^{-19}$.

[3] Comparison of the petit mal subdivision to the subdivision composed of cases with seizures other than petit mal within the SSW subgroup in respect to breech delivery reveals $X^2 = 6.8$, $V = 1$, and $P = 9.1 \times 10^{-3}$.

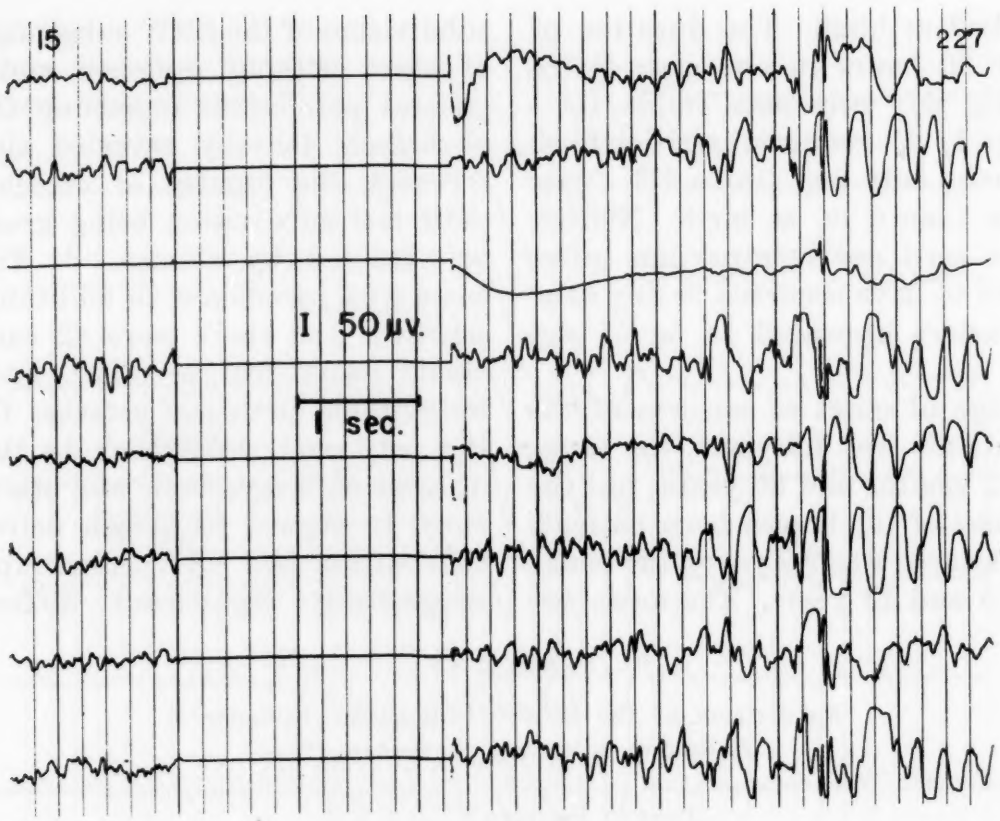

Fig. 4
EEG of child with observed petit mal attacks. Onset age 5. Electrode arrangement A.

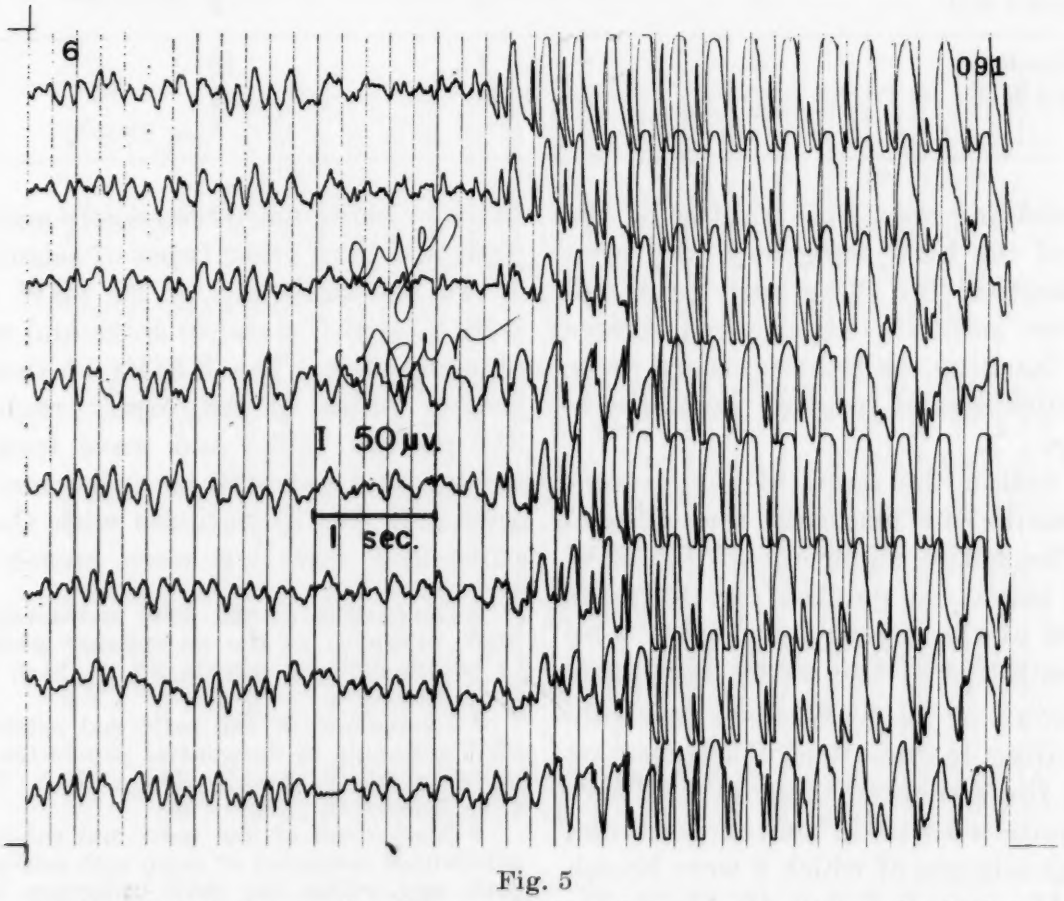

Fig. 5
EEG of breech born twin with myoclonic and grand mal seizures beginning at age 7. Electrode arrangement B.

viduals (table III — cases 3, 6, 12, 16, 27; fig. 1, 3, 4, 6). Comparison of the cases with "classical spike and wave" discharges to the group of cases without epilepsy and also to the general population revealed that the number of breech born individuals was significantly greater in the group of "classical spike and wave" cases than in the group without epilepsy [1] or in the general population.[2]

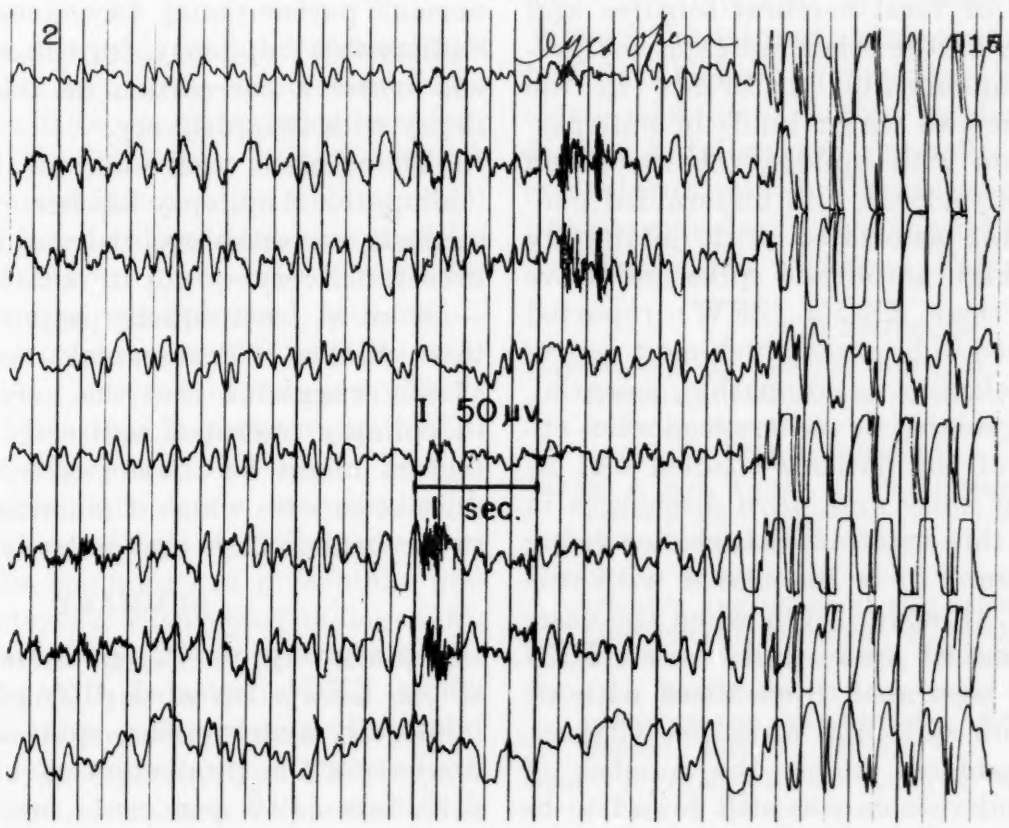

Fig. 6

EEG of patient with observed petit mal attacks beginning at age 13. Electrode arrangement A.

DISCUSSION

The spike and wave phenomenon is not altogether unique to cases considered to have "idiopathic" epilepsy, for it has been observed in cases following encephalitis (Gibbs and Gibbs 1956), and in oligophrenic phenylpyruvia (Fois *et al.* 1955). EEG's containing diffuse spike and waves have been described by Penfield and Jasper (1954) in patients who were found to have epileptogenic foci situated on the mesial surface of the frontal lobe. Myoclonic seizures have been described in cases with myoclonus epilepsy of Unverricht (Grinker *et al.* 1938; Unverricht 1895; van Bogaert 1929). Furthermore, the spike and wave phenomenon has been induced in dogs by means of fluoracetic acid (Chenoweth and St. John 1946). It seems best, at present, to consider the diffusely distributed bilaterally synchronized spike and wave EEG phenomenon and the seizures associated with this type of disturbance as manifestations of disturbed cerebral physiology which can be induced by several agencies.

Originally, the author tried to find whether there was a correlation between a particular mode of birth and focal cerebral seizures, particularly temporal lobe epilepsy, since Earle, Baldwin and Penfield (1953) demonstrated how atrophic lesions in the temporal lobe could be produced by herniation of this

[1] Comparison of "classical spike and wave" cases to the no epilepsy group in respect to breech delivery reveals $X^2 = 12.4$, $V = 1$, and $P = 4.3 \times 10^{-3}$.

[2] Comparison of "classical spike and wave" cases to the general population in respect to breech delivery reveals $X^2 = 42.4$, $V = 1$, and $P = 7.5 \times 10^{-11}$.

part of the brain beneath the tentorium. So far no correlation to any particular mode of delivery and seizures of temporal lobe or other focal origin has been found. Instead a positive correlation between breech delivery and "idiopathic" epilepsy was found. The finding of a strong correlation of "idiopathic" epilepsy with breech delivery on the one hand, but no correlation of focal cerebral seizures and breech delivery on the other indicates the presence of a fundamental difference in the origins of these two major kinds of epilepsy.

The patients with epilepsy characterized by petit mal, myoclonic, and unheralded generalized seizures associated with bilaterally synchronized high amplitude spike and wave discharges in their EEG's (SSW) reported here are believed to be cases which most neurologists would classify as idiopathic, essential, cryptogenic, genetic, or centrencephalic epilepsy. Some of the patients studied had irregular or slow spike and wave discharges in their EEG's, this type of disturbance being regarded by some to be associated with cerebral damage. However, even when the cases with the "classical spike and wave" EEG reaction were separated from those with irregular and slow spike and wave disturbances, and were considered alone, the number of breech born individuals was still found to be greater than would be expected by chance. Likewise the number of breech born individuals among those with petit mal seizures was greater than would be expected by chance. In fact the evidence suggests that breech delivery is more frequent in patients with petit mal attacks than in those with myoclonic and other kinds of seizures.

The significantly large number of breech born individuals in this group of "idiopathic" epilepsy cases (approximately 20 per cent) cannot be explained reasonably by mechanisms other than those including breech delivery as an important factor leading to cerebral damage. How the brain may be damaged through breech delivery cannot be ascertained by means of this study; nor is there any suggestion as to what complications of breech delivery might result in the disease. Conceivably asphyxia could be the cause as Nielsen and Courville (1951) suggest. Tentorial tears and asphyxia neonatorum are reportedly the most common causes of death from breech delivery in the full term infant (Holland 1922). Perhaps distortion of the brain or brain stem causes injury which lays the foundation for the development of "idiopathic" epilepsy. Breech delivery is not the only abnormal parturitional factor associated with "idiopathic" epilepsy, for the author recently has found a correlation of this type of epilepsy with twin delivery.

The genetic influence in the origin of "idiopathic" epilepsy has been repeatedly described; nevertheless, it would appear that breech delivery — not to mention twin births — is an at least equally important factor in this disease. Pasamanick and Lilienfeld (1955) suggested that the hereditary factors in epilepsy operated indirectly in that these factors might be those governing the reproductive process which if abnormal could result in cerebral damage and epilepsy.

SUMMARY

In a group of (92) patients with epilepsy whose EEG's revealed diffusely distributed, bilaterally synchronous, spike and slow wave discharges the proportion of breech born individuals (19.6 per cent) was found to be significantly greater than the proportion of breech birth (3.4 per cent) in the general population. In contrast, the proportion of breech born individuals (2.8 per cent) in a group of epileptic patients with localized EEG disturbances did not differ significantly from that in the general population. The proportion of breech born in a group of (20) patients who had petit mal seizures and also in a group of (20) patients with "classical spike and wave" was significantly greater than that in the general population. The high incidence of breech birth in patients who have epilepsy of the type associated with bilaterally synchronous spike and wave EEG disturbances strongly suggests that breech delivery is an important factor in the pathogenesis of this disorder. Breech delivery does not appear to be an important factor in the origin of focal cerebral seizures.

RÉSUMÉ

Dans un groupe de 92 malades dont l'EEG présentait des décharges ''pointe-onde'' à distribution diffuse, bilatérale et synchrone, on a remarqué que la proportion de délivrances par le siège (19,6 pour cent) était plus élevée d'une manière significative que la proportion de délivrances par le siège dans une population globale (3,4 pour cent). Au contraire, dans un groupe de malades épileptiques présentant des anormalités électroencéphalographiques localisées, la proportion de délivrances par le siège (2,8 pour cent) ne variait pas de manière significative de la proportion de délivrances par le siège dans une population globale. Dans un groupe de 20 malades qui avaient des attaques du type ''petit mal'', ainsi que dans un groupe de 20 malades avec des anormalités électroencéphalographiques ''pointe-onde'' classique la proportion de délivrances par le siège était plus élevée de manière significative que pour la population globale. L'incidence élevée de délivrances par le siège chez des malades qui présentent une épilepsie caractérisée électroencéphalographiquement par des pointes-ondes bilatérales synchrones suggère que la délivrance par le siège joue un rôle important dans sa pathogenèse. La délivrance par le siège d'autre part ne semble pas être un facteur important dans la genèse d'une épilepsie focale.

ZUSAMMENFASSUNG

Es wurde festgestellt, dass in einer Gruppe von 92 Epileptikern, deren Elektroenzephalogramme diffus verteilte bilateral synchrone ''spike and wave'' Entladungen aufwiesen, der Prozentsatz von Individuen, die in Steisslage geboren worden waren (19.6 Prozent) signifikant höher war als der Prozentsatz von Steissgeburten (3.4 Prozent), welche man in der Allgemeinbevölkerung antrift. Im Gegensatz dazu wurde gefunden, dass in einer Gruppe von Epileptikern mit lokalisierten elektroenzephalographischen Störungen die Häufigkeit von Individuen, welche in Steisslage geboren worden waren (2.8 Prozent), keinen signifikanten Unterschied aufwies zu derjenigen, wie sie in der Allgemeinbevölkerung angetroffen wird. Die Häufigkeit von Steissgeburten in einer Gruppe von 20 Patienten mit Petit Mal-Anfällen und in einer Gruppe von 20 Patienten mit klassischen ''Spike-and-Wave'' Entladungen war in signifikanterweise grösser als in der Allgemeinbevölkerung. Die hohe Inzidenz von Steissgeburten, welche bei Epileptikern angetroffen wird, die an einem Anfallstypus leiden, welcher mit bilateral synchronen ''Spike-and-Wave'' Entladungen einhergeht, weist darauf hin, dass Geburt in Steisslage wahrscheinlich einen wichtigen Faktor in der Pathogenese dieser Anfallstypen darstellt. Andererseits erscheint es unwahrscheinlich, dass Geburt in Steisslage in der Genese von fokalen zerebralen Anfällen einen wichtigen Faktor darstellt.

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PRINTED IN CANADA

THE SPIKE AND WAVE COMPLEX; A CLINICAL CORRELATION

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(Received for publication: December 10, 1957)

The spike and wave pattern is one of the most striking abnormalities in the electroencephalogram. It was already in 1935 (Gibbs, Davis and Lennox) associated with petit mal seizures, and Gibbs, Gibbs and Lennox (1943) referred to this discharge as the petit mal pattern. There has, however, been some disagreement in the literature as to its clinical significance (Jasper and Kershman 1941; Silverman 1954; Clark and Knott 1955; Howell 1955; Haugsted and Höncke 1955).

As a contribution to this problem 10.000 consecutive EEG-records taken in the period from April 1952 to October 1954 at the Neurophysiological Laboratory, Rikshospitalet, Oslo University, were reviewed for the presence of spike and wave patterns. In this material spike and wave abnormalities were found in routine examination, without Metrazol, photic or sleep activation, in 833 EEG-records of 363 patients.

As the spike and wave patterns showed marked electrical differences, an attempt was made to classify them in various groups. The different spike and wave abnormalities in 18 such subgroups were at first correlated with the seizure patterns as well as with the clinical data. The correlation showed no significant discrepancy between female and male, nor any discrepancy between some of the other subgroups. We preferred, therefore, to divide the spike and wave records in the four following subgroups only, showing the most marked differences: A, B, C, D. (Table I.)

TABLE I

EEG classification	No. of EEGs	No. of Patients
A. 3/sec. spike and wave	106	46
B. Other spike and wave with normal background activity	232	119
C. Other spike and wave with pathological background activity	388	148
D. Focal spike and wave complexes only	107	50
Total	833	363

Group A. Well-regulated paroxysmal "classical" 3/sec. spike and wave discharges, bilaterally synchronous with frontal maximum (fig. 1).

Group B. Paroxysmal spike and wave discharges, bilaterally synchronous with other frequences than 3/sec. or with multiple spikes or with more irregular spike and wave complexes. The background activity was normal in this group (fig. 2).

Group C. The same spike and wave patterns as in group B, but with pathological background activity (fig. 3).

Besides the spike and wave activity in groups A, B and C there were in some of the records also focal discharges.

Group D. Focal spike and wave activity of various forms (fig. 4).

The age of the patients in the various subgroups at the time of examination as well as the age at the onset of seizure is seen from table II.

In nearly 40 per cent of all cases the seizures started before the age of 5 years (table II). This onset in childhood is more pronounced in group D with focal spike and wave activity and in group C with irregular spike and wave pattern and pathological background activity than in the groups A and B. None of the patients with the classical spike and wave pattern was recorded electroencephalographically before reaching the age of 5 years, while in group B, 6 per cent, and in the group C and D, 12 per cent, were examined before the same age. Before the age

of 10 years, 24 per cent in group A, 26 per cent in group B, 41 per cent in group C, and 50 per cent in group D, were registered with EEG.

Out of the 363 patients with spike and wave pattern in their EEG-records, 215 patients, or nearly 60 per cent, had some etiological factors in their case history. Among these 87 patients, about 24 per cent, had a positive family history of epilepsy. The presumed etiological factors are shown in table III.

In 2 of the 4 patients with focal spike and wave pattern in the EEG and intracranial tumor, the tumors were located in the cerebral hemispheres. A 41 year old man, who had never had any seizure, showed electroencephalographically, focal spike and wave activity in the left temporal region. The operation revealed a glioma in the same area.

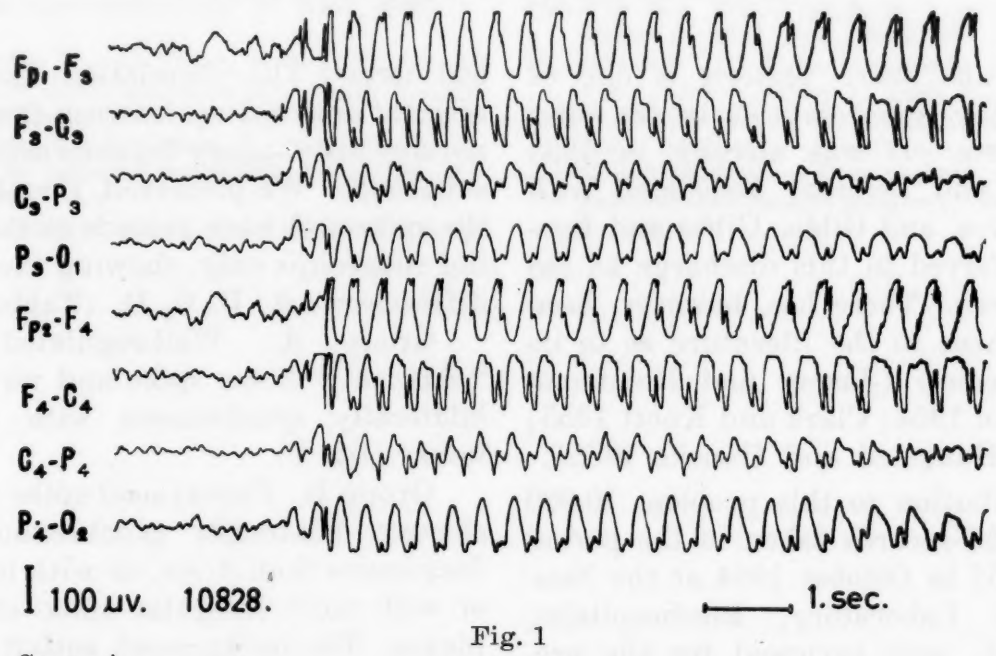

Fig. 1

Group A.
''Classical'' spike and wave pattern. Time marker — 1 sec.

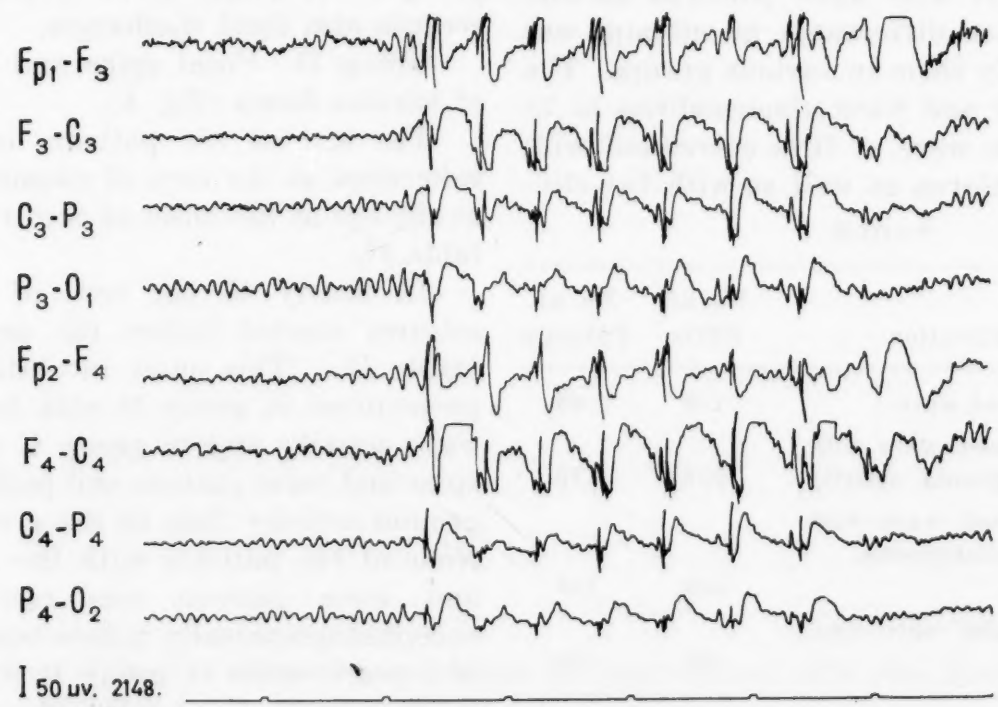

Fig. 2

Group B.
Irregular spike and wave pattern with normal background activity. Time marker — 1 sec.

A woman, 50 years old, with some grand mal seizures in her case history, had an astrocytoma in her left frontal region and focal spike and wave activity in the same area in the EEG.

Two boys, 14 and 7 years old, had focal spike and wave patterns in their EEG-records, both in the right parietal region. One had focal seizures characterised with start in the left arm. The other had never had seizures.

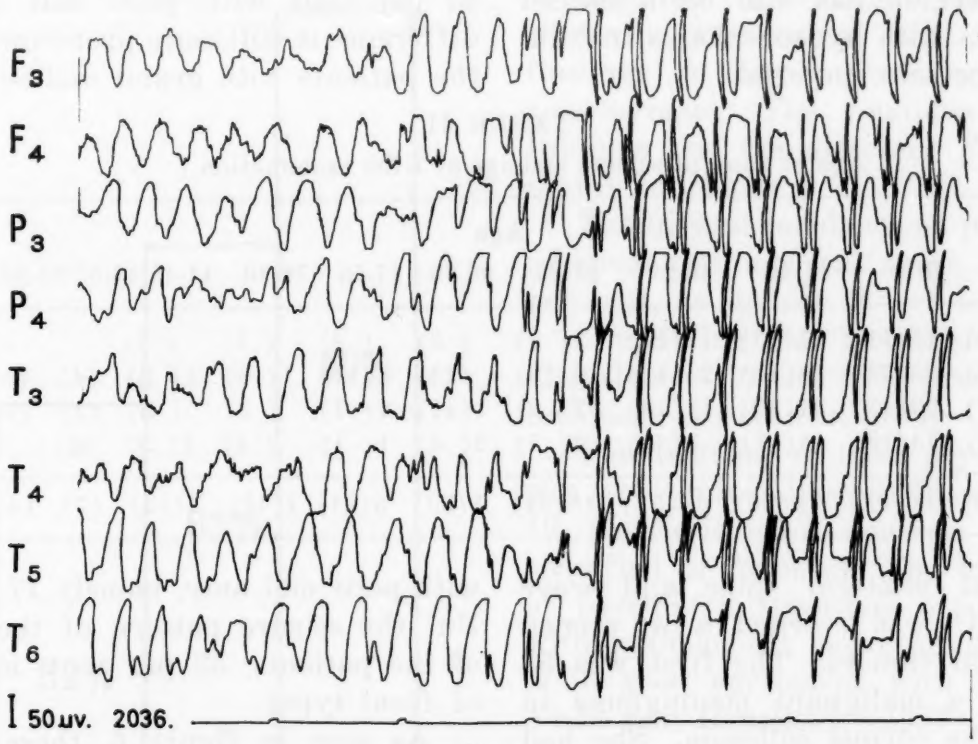

Fig. 3

Group C.
Irregular spike and wave pattern with pathological background activity. Time marker — 1 sec.

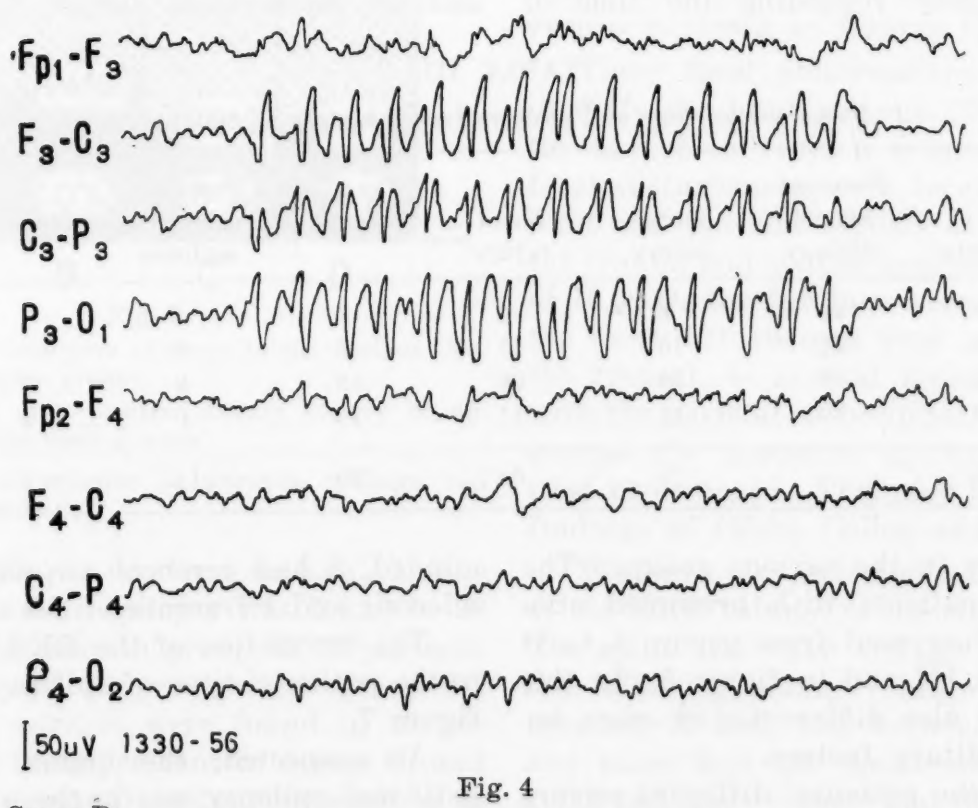

Fig. 4

Group D.
Focal spike and wave activity. Time marker — 1 sec.

They both had hydrocephalus, in one caused by an astrocytoma in the cerebellum, and in the other by a medullablastoma in the region of the fourth ventricle.

Such focal spike and wave activity in the right parietal region has also been noticed in other patients with hydrocephalus, not included in the present material.

tion to the EEG classification is shown in figure 7.

Figure 6 yields some interesting information. Primarily it is remarkable that 80 per cent of the patients had grand mal against 43 per cent with petit mal epilepsy. The difference is still more pronounced if we count the patients with grand mal as against those

TABLE II

Age at onset of seizure and age at EEG examination ( )

	Age													
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70
Group A.	15(0)	15(11)	11 (13)	2(12)	3(4)	(2)	(2)	(1)	(1)					
Group B.	30(7)	23(19)	26(12)	21(17)	9(19)	(13)	2(11)	1(6)	2(3)	(4)	(3)	(4)	(1)	
Group C.	66(17)	29(43)	31(30)	13(18)	1(8)	1(11)	2(7)	(3)	(5)	(1)	(1)	(3)		(1)
Group D.	23(6)	13(19)	4(7)	3(4)	2(3)	2(4)	1(1)	(1)	1(3)	(2)				
Total	134(30)	80(92)	72(62)	39(51)	15(34)	3(30)	5(21)	1(11)	3(12)	(7)	(4)	(7)	(1)	(1)

The atypical bilateral spike and wave pattern (group C) was recorded in two women with intracranial tumors. The first was 55 years old with a malignant meningioma in the region of the corpus collosum. She had no seizures. The other was 14 years old, had grand mal and a tumor in the posterior fossa.

From table III it appears that there is the same tendency regarding the time of

with petit mal only, namely 17 to 5 per cent. But the seizure pattern of the greater part of the patients, 52 per cent, mainly consists of focal types.

As seen in figure 6, there were, all together, 11 patients with spike and wave discharges in their EEG-records who had never had epileptic seizures. Of these patients 3 had an intracranial tumor, 3 were feeble-

TABLE III

Presumed etiology and positive family history of epilepsy

EEG groups	Nos. of patients	Per cent known etiology	Birth injury	Head injury	Infection	Vascular abnormalities	Tumor	Epilepsy in family
A.	46	43	6	6	2			8
B.	119	52	16	27	6	2		29
C.	148	63	39	20	12	8	2	38
D.	50	80	11	11	10	4	4	12
Total	363		72	64	30	14	6	87

onset of seizures in the various groups. The percentage of patients with presumed etiological factors increased from group A to D as seen in table III and in figure 5. In this figure we have also differentiated more between the hereditary factors.

A study of the patients' different seizure patterns is shown in figure 6 and their rela-

minded, 2 had cerebral atrophy, 2 multiple sclerosis and 1 fracture of the skull.

The correlation of the EEG abnormalities to the patients' type of epilepsy is seen from figure 7.

As suspected, the highest incidence of petit mal epilepsy was in the group with the classical spike and wave (group A), but it

is remarkable that this same group had a high incidence of focal epilepsy as well. Out of the 46 patients in this group 26 per cent had focal motor seizures, 7 per cent focal sensory, 13 per cent autonomic, 7 per cent psychical seizures and 28 per cent automatism. In the other groups motor epilepsy was found in 28 per cent of the cases in group B, 42 per cent in group C, and 32 per cent in group D; focal sensory seizures were found in 10 per cent in group B, 8 per cent in group C, and 6 per cent in group D; autonomic seizures in 11 per cent in group B, 16 per cent in group C, and 12 per cent in group D; psychical seizures in 7 per cent in group B, 5 per cent in group C, 8 per cent in group D; automatism in 9 per cent in group B, 7 per cent in group C, 6 per cent in group D.

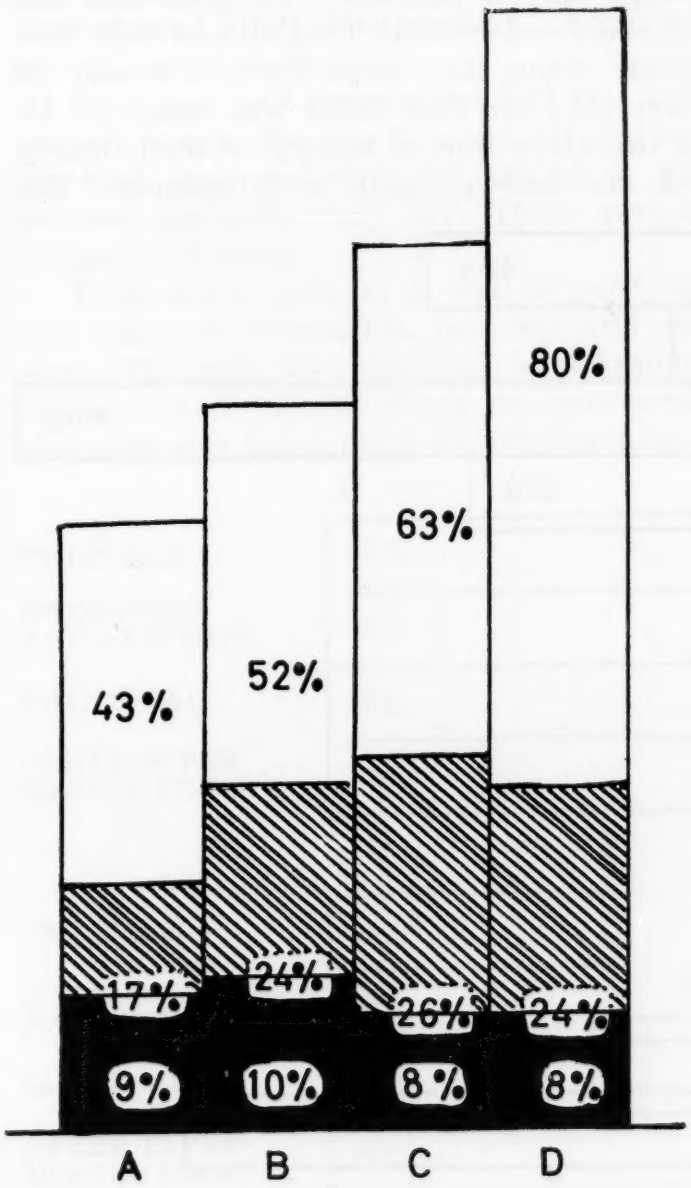

Fig. 5

Incidence of presumptive etiology in the various electroencephalographic groups.

Incidence of a positive family history of epilepsy in the same groups.

History of seizures in parents, siblings and grandparents only.

Some of the patients had neurological clinical symptoms as well as pathological findings in their pneumoencephalograms or arteriograms. The relations between these findings and the different EEG groups are shown in figure 8.

The highest incidence of pathological neurological findings was again in group D, 96 per cent, as against 26 per cent in group A.

Correlating the incidence of psychiatric disturbances to the EEG-groups, the highest incidence is found in group C (see fig. 9).

The diagnosis of these psychiatric patients was feeble-mindedness in 78 cases, dementia in 19, psychosis in 7, neurosis in 13 and unclassified in 29 cases. The highest incidence of psychiatric disorders occurs in group C with pathological background activity. This is in good agreement with the findings of Vislie and Henriksen (1957).

In all the subgroups we have, beside the spike and wave abnormalities, some bursts of focal disturbances as well. The relation between these focal abnormalities and the subgroups is shown in figures 10 and 11.

These focal abnormalities were localized in different head regions (fig. 12). Before the age of 15 years a greater part of these focal disturbances were located in the occipital and parietal regions as compared with the frontal and central regions. After the age of 15 years the findings were quite different; the focal disturbances were now dominant in the frontal + central regions as compared with the parietal + occipital, but in both age groups the temporal dysrhythmia was the most pronounced. This may be related to the findings of Gibbs, Gillen and Gibbs (1954).

We have also investigated the correlation of the EEG voltage to the clinical symptoms. The spike and wave voltage was grouped in the following manner: below 75 microvolts, between 75 and 150, between 150 and 250, and more than 250 microvolts. Between the spike and wave voltage and the clinical symptoms and epileptic seizure pattern we could

find no significant correlation. The same was the case when the EEG disturbances were correlated with the number of epileptic seizures, which were divided in dayly, weekly, monthly and yearly seizures.

Particular interest is attached to group A, the patients with EEG disturbances showing exactly 3/sec. bilaterally synchronous spike and wave discharges with maximum over the frontal regions. This spike and wave pattern was of the highest voltage and came, in our opinion, as close to the classical ''petit mal'' spike and wave pattern as possible. However, only 12 of the patients in group A had EEG-records showing bilaterally synchronous spike and wave discharges without pathological background activity and without focal disturbances. These 12 patients had the following clinical symptoms and signs.

They were 6 female and 6 male, and all together 34 EEG-records were taken. Three of the patients had had their first seizure before the age of 5 years, 6 before 10 years of age and 3 between their 11th and 15th years.

Petit mal alone was very rare in this group; only 3 patients (two girls and one boy) suffered from it. They all had their first seizure when they were between 5 and 10 years old; the first EEG was taken at 15. In two there were a history of birth injury and one had a cousin with epilepsy. The pneumoencephalograms of both girls were normal.

Grand mal seizures alone had the fourth patient of this group, a boy. Five EEGs were obtained between the age of 11 and 15 years, always with the classical spike and wave pattern with no other pathological disturbances. He had his first convulsions before the age of 5, and no etiological factors could be traced.

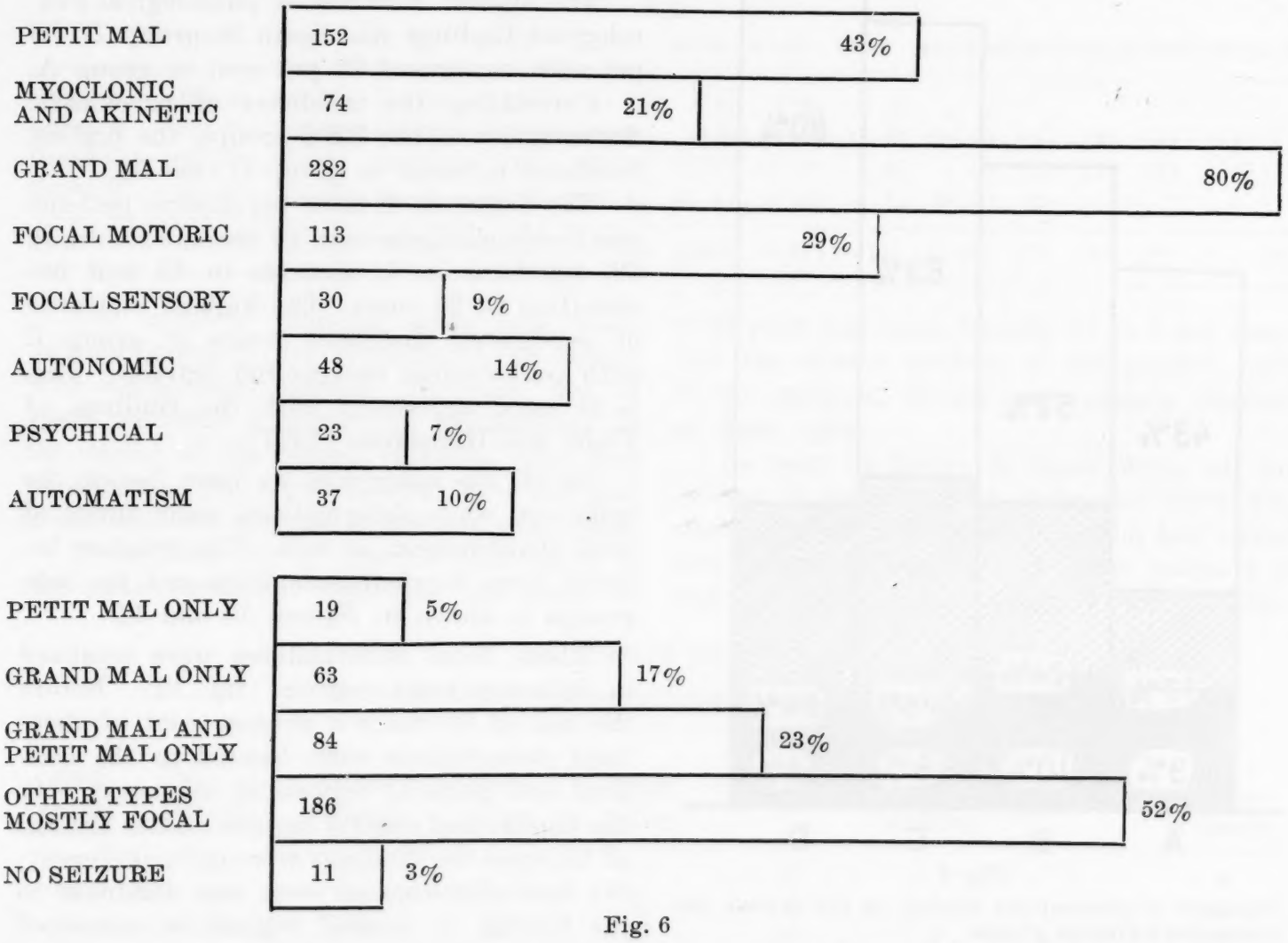

Fig. 6

Types of seizure pattern in 352 cases with spike and wave discharges

Grand mal and bilateral myoclonic jerks had the fifth patient, a boy. The seizures started before he was 10 years old. He had about one convulsion a month and was not examined neurologically and with EEG before the age of 14. His pneumoencephalogram then showed a left-sided atrophy. There was no etiological factors.

Petit mal and automatism had the sixth patient, a boy. He was 15 years old and had his first seizures before the age of 5. His seizures appeared every day. There were no etiological factors.

Focal motor seizures as well as petit mal had the next 3 patients, one boy and two girls. The girls both had had head trauma, one as a birth injury. Their pneumoencephalograms were normal and the arteriograms in one case were also normal. They all had seizures every day and their first convulsion occurred in one case before the age of 5, in one between her 5th and 10th year and in the last between his 10th and 15th year.

Petit mal, grand mal, as well as automatism, had the last 3 patients of the group, which consisted of one man and two women. The seizures started before the age of 15 in all cases. The man was 35 years old when he was examined. He then showed psychic disturbances, but the neurological examination was otherwise normal. One of the women had paresis of the right leg after the seizures, and the pneumoencephalograms of the other were abnormal with atrophy of the left hemisphere. They were both about 20 years at the time of examination.

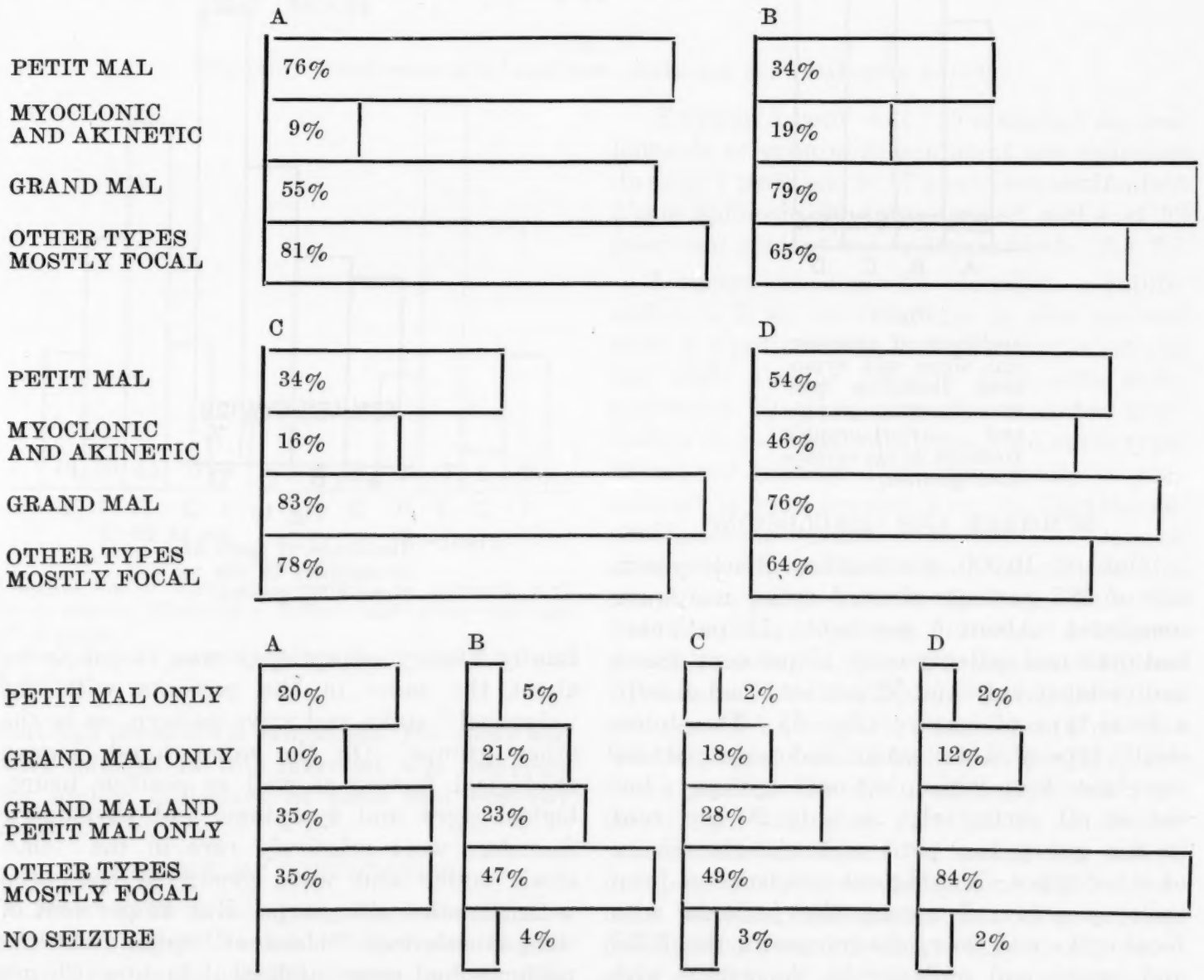

Fig. 7
EEG classification and types of seizure

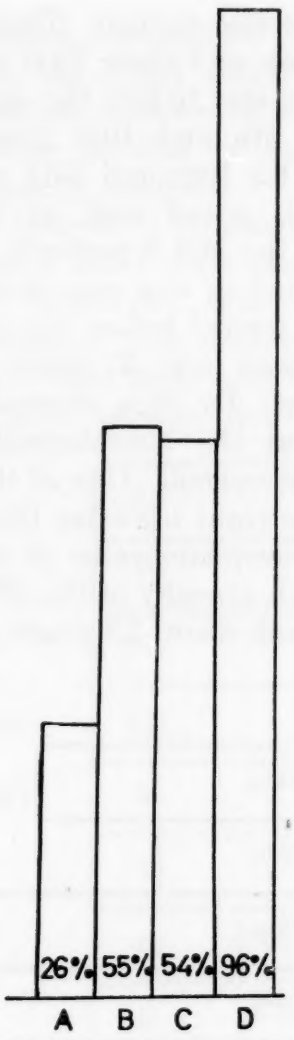

Fig. 8

Incidence of neurological signs and symptoms including positive encephalographic and arteriographic findings in the various EEG-groups.

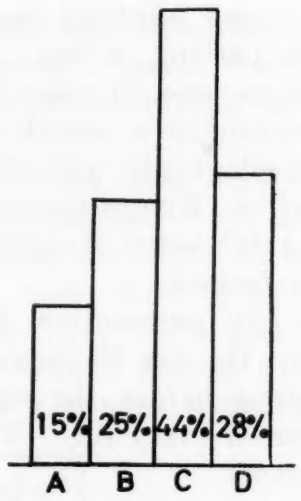

Fig. 9

Incidence of psychiatric findings in the various EEG groups.

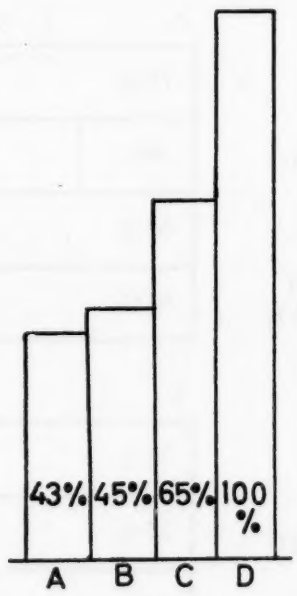

Fig. 10

Incidence of focal abnormalities in the various EEG groups.

SUMMARY AND CONCLUSIONS

Out of 10,000 consecutive EEG-records 833 of 363 patients showed spike and wave complexes. About 5 per cent (19 patients) had petit mal epilepsy only, 17 per cent grand mal epilepsy only and 52 per cent had chiefly a focal type of seizure (fig. 6). The ''classical'' type of 3/sec. spike and wave pattern correlates best with petit mal epilepsy, but not at all exclusively, as only 20 per cent in this group had petit mal without seizure of other types. The highest incidence of focal epilepsy occurred among the patients with focal spike and wave discharges in the EEG and grand mal epilepsy in the group with irregular spike and wave complexes. A positive family history of epilepsy was found to be about the same in the patients with the ''classical'' spike and wave pattern, as in the other groups. On the other hand, known etiological factors as well as positive neurological signs and symptoms and psychiatric disorders were relatively rare in the ''classical'' spike and wave group as compared with the other subgroups. But 43 per cent of the patients with ''classical'' spike and wave patterns had some etiological factors; 26 per cent had positive neurological signs and 15 per

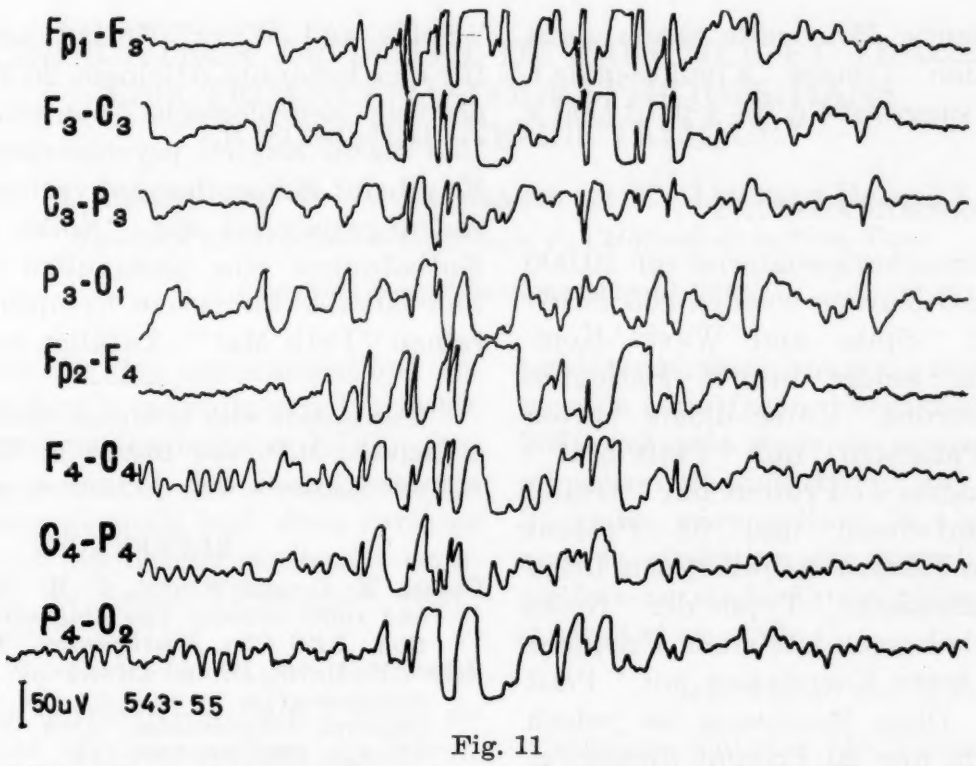

Fig. 11
Bilaterally synchronous spike and wave discharges and focal spike activity.

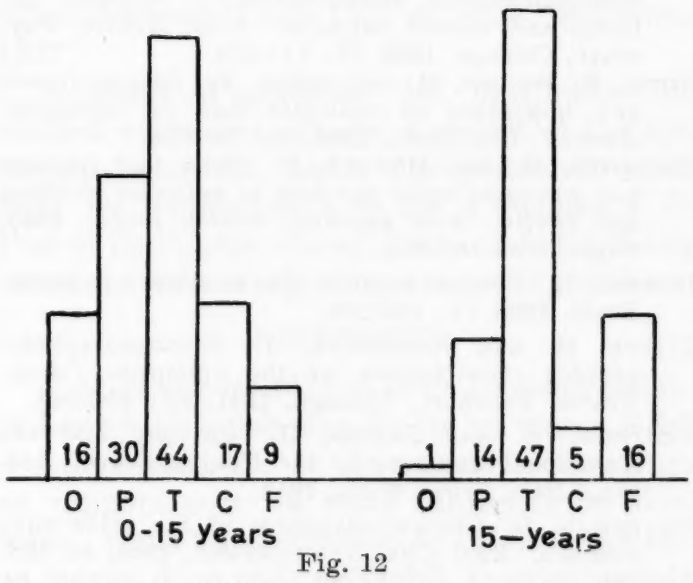

Fig. 12
Localization of EEG abnormalities in patients with focal seizure discharges before and after the age of 15 years.
O occipital, P parietal, T temporal, C central and F frontal.

cent had psychiatric symptoms. The spike and wave pattern in this material was therefore not highly indicative of petit mal epilepsy alone.

RÉSUMÉ ET CONCLUSIONS

Huit cent trente-trois électroencéphalogrammes, appartenant à 363 malades, et pris d'un groupe de 10.000 traces consécutifs, montraient des complexes pointe-onde.

Environ 5 pour cent (19 malades) des malades de ce groupe présentaient une épilepsie du type « petit mal », 17 pour cent souffraient d'une épilepsie du type « grand mal » et 52 pour cent avaient une épilepsie focale (fig. 6).

L'image classique du complexe « pointe-onde » à 3/sec. se rencontre le plus souvent dans le « petit mal » ; ceci pourtant n'est pas une règle absolue puisque dans cette série, seulement 20 pour cent des malades souffraient de petit mal sans crise d'un autre type. Parmi ces malades l'épilepsie focale se rencontrait le plus souvent avec un électroencéphalogramme à pointe-onde localisée. Dans ce groupe le « grand mal » était associé avec des complexes pointe-onde irréguliers. Une histoire familiale d'épilepsie était aussi fréquente parmi les malades qui présentent un complexe « pointe-onde » classique, que parmi les autres groupes. D'autre part, l'incidence d'un facteur étiologique connu aussi bien que de symptômes positifs d'ordre neurologique ou psychiatrique était plus rare parmi le groupe pointe-onde classique que parmi les autres groupes. On pouvait néanmoins déceler certains facteurs étiologiques chez 43 pour cent des malades avec une image classique « pointe-onde » ; 26 pour cent avaient des signes neurologiques positifs, et 15 pour cent des symp-

tômes psychiatriques. Pour cette raison, dans cette investigation l'image « pointe-onde » n'était pas très suggestive d'un « petit mal » pur.

ZUSAMMENFASSUNG

In einem Untersuchungsmaterial von 10.000 konsekutiven EEG-Kurven wurden 833 EEG-Aufnahmen mit ''Spike and Wave''-Komplexen gefunden, welche in 336 Patienten aufgenommen wurden. Unter diesen hatten 5 Prozent (19 Patienten) nur ''Petit Mal''-Anfälle, währenddem 17 Prozent nur ''Grand Mal''-Anfälle aufwiesen und 52 Prozent hauptsächlich an fokalen Anfallstypen litten (fig. 6). Der ''klassische'' Typus der ''Spike and Wave''-Entladungen mit einer Frequenz von 3 Hz. zeigt beste Korrelation mit ''Petit Mal''-Epilepsie. Diese Beziehung ist jedoch nicht exklusiv, da nur 20 Prozent dieser Patientengruppe ''Petit Mal''-Anfälle ohne andere Anfallstypen hatten. Die grösste Zahl fokaler Anfälle wurde bei Patienten beobachtet, in denen die ''Spike and Wave''-Entladungen fokal auftraten und ''Grand Mal''-Epilepsie war am häufigsten anzutreffen bei Patienten, welche unregelmässige ''Spike and Wave''-Entladungen aufwiesen. Eine positive Familienanamnese auf Epilepsie wurde ungefähr gleich häufig angetroffen bei Patienten mit klassischen ''Spike and Wave''-Entladungen wie in den anderen Gruppen. Andererseits waren bei Patienten mit klassischen ''Spike and Wave''-Entladungen die ätiologischen Faktoren im allgemeinen nicht bekannt. Neurologische Symptome und psychiatrische Störungen waren ebenfalls selten in diesen Patientengruppen. Immerhin hatten 43 Prozent der Patienten mit klassischen ''Spike and Wave''-Entladungen Anzeichen für eine bekannte Ätiologie, 26 Prozent wiesen positive neurologische Symptome auf und 15 Prozent zeigten psychiatrische Störungen. Es scheint daher, dass im vorliegenden Untersuchungsmaterial die ''Spike and Wave''-Entladungen eine nicht allzu enge Korrelation mit der klinischen Symptomatologie von reinen ''Petit Mal'' -Anfällen aufwiesen.

The authors wish to express their thanks to prof. S. Refsum, M.D. and Docent B. Kaada, M.D. for valuable assistance with the manuscript.

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PRINTED IN CANADA

INDICATEUR DE L'ÉTAT DE PRÉSENCE ET TRACÉS ÉLECTROENCÉPHALOGRAPHIQUES DANS LE SOMMEIL NEMBUTALIQUE [1]

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(Received for publication: May 13, 1958)

L'enregistrement des communications sujet-observateur dans le cadre de la polygraphie (EEG, ECG, rythme respiratoire, EDG), étudié à la Pitié, a fourni des renseignements dans les absences de petit mal, dans certains troubles mentaux des lésions cérébrales organiques et dans les comas (Fischgold 1957; Fischgold et Mathis 1957).

Ce travail se limite à l'application des communications enregistrées, dans l'étude de l'endormissement du sommeil et du réveil nembutaliques qui ont été envisagés dans sa thèse inaugurale par l'un de nous (Schwartz 1957).

Il s'agit d'apprécier les possibilités de contact entre le sujet qui s'endort et l'observateur, selon les stades électriques de sommeil, les « questions » et les « réponses » de l'un et de l'autre s'inscrivant sur le tracé aux moments mêmes où elles sont « exprimées ».

HISTORIQUE

Dès les années 1938 et 1939, Davis et collab. et Loomis et collab. ont étudié les tracés EEG d'endormissement et de sommeil spontanés en rapport avec les états subjectifs du dormeur. Dans les recherches de Davis et collab., au moyen d'un code préétabli, le sujet signale sur son tracé la sensation de « flottement » vers le sommeil, ou la sensation de réveil, dès qu'il en est conscient. Les auteurs rattachent le « flottement » à l'aplatissement du tracé qui peut durer de 1,5 à 5 sec.; le « flottement » est signalé par le sujet entre 0 et 5 sec. après le retour de son alpha.

Loomis et collab. évaluent la capacité du sujet de répondre à des stimuli acoustiques, lumineux ou douloureux envoyés à des temps prédéterminés au cours du sommeil. Ils décrivent de cette façon divers modes de réactivité EEG selon le stade de sommeil où tombe le stimulus: réaction d'arrêt sur le rythme alpha de veille, réapparition de l'alpha s'épuisant avec la répétition des stimuli au stade B et parfois au stade C, complexe K à la fin du stade B et au stade C.

MATÉRIEL DE MALADES

Quinze malades (16 tracés) fournissent le matériel de ce travail. Leurs tracés de veille ne représentent que de discrètes anomalies EEG et les enregistrements de sommeil sont demandés pour « activation ». Deux sujets sont des comitiaux connus, six suspects de comitialité, cinq des traumatisés du crâne (dont deux suspects de comitialité post-traumatique) ; un sujet se plaint de somnolence diurne, le dernier présente un syndrome de Little. Ils sont âgés de 10 à 55 ans. Dans un seul tracé, le sommeil révèle des altérations électriques inapparentes dans la veille.

TECHNIQUE D'EXAMEN

Le sommeil spontané n'ayant pu être obtenu, le Nembutal est administré aux doses de 120 à 300 mg. par voie buccale ou rectale après le début du tracé.

Les 15 dérivations d'un électroencéphalographe Alvar sont ainsi employées: 10 dérivations pour l'EEG (montage bipolaire longitudinal, constante de temps 3/10 sec., sans filtre) ; une dérivation pour l'ECG, une pour la respiration, une pour l'inscription du stimulus lumineux, une pour l'inscription de la réponse du sujet au flash, une pour l'électrodermogramme (EDG) enregistré selon la méthode décrite par D. Albe-Fessard (1954).

Le stimulus lumineux fourni par un stroboscope placé à 25 cm. du visage du sujet est

[1] Travail réalisé avec une subvention des Laboratoires Abbott.

[2] Chargé de recherches à l'I.N.H.

envoyé par l'observateur à des temps irréguliers, dès que le tracé indique les signes d'endormissement ou si on désire réveiller le malade ; le stimulus lumineux s'accompagne d'un « clic » auditif qui intervient également dans les réactions d'éveil.

Le sujet étant confortablement allongé, la seule consigne donnée est de répondre dès qu'il perçoit le stimulus lumineux en appuyant deux fois sur le bouton du boîtier attaché à sa main droite. Un minimum d'instruction est donné au malade pour ne pas créer un état d'alerte. Afin d'avoir une indication des modifications du tonus musculaire, on ne demande pas au malade de fermer les yeux ; on peut dans ces conditions assister à la chute progressive des paupières avec l'approche du sommeil. Les artefacts myographiques renseignent sur le tonus musculaire général.

Nous n'insisterons pas sur les modifications cardio-respiratoires (ralentissement avec l'endormissement et le sommeil, accélération avec le réveil), sur les variations de l'EDG (augmentation de la résistance cutanée — RC — avec l'endormissement, réponses EDG quand l'alpha existe ou reparaît), sur le temps mis par les sujets à s'endormir, sur les rythmes rapides nembutaliques ou sur les modifications du tonus. Ces faits — en partie connus — ont été étudiés dans ces tracés mais n'entrent pas directement dans le cadre de cet article (Schwartz 1957).

Nous nous attacherons par contre à *« l'indicateur de l'état de présence » c'est-à-dire aux communications enregistrées qui permettront au sujet de montrer sa présence vigile par des signaux émis après la perception du flash.*

TABLEAU I

Types de sommeil	Nombre de malades	Signes EEG de sommeil	Comportement aux stimuli du TR	Comportement somatique	Comportement végétatif	Appréciation subjective
I	3	+	+	+	+	+
II	1	+	+	+	+	—
III	1	+	—	+	+	—
IV	1° partie 2	+	+	+	+	+
	2° partie	—	+	+	+	+
V	1	—	+	+	—	±
VI	2	+ très courts	—	—		
VII	2	+ décharges de PO	+	+	+	+
VIII	4	—	—	—	—	—

\+ qualifie tout ce qui est comportement de sommeil confirmé.
— qualifie tout ce qui est comportement de veille.

Au début, nous avons parlé de « temps de réaction » (TR) puisque cette méthode peut être rapprochée du TR des psycho-physiologistes. Elle diffère cependant de ce dernier par plusieurs points essentiels.

TR des psychophysiologistes

1 — étudié dans la veille
2 — long entraînement
3 — avant signal « prêt »

Observation I (figures 1, 2, 3, 4)

ENDORMISSEMENT AVEC ARRÊT DES RÉPONSES

Malade de 24 ans présentant des crises céphalalgiques depuis un traumatisme crânien survenu 1 mois avant l'enregistrement.

YF = yeux fermés, YO = yeux ouverts, Resp. = respiration, ECG = électrocardiogramme, Stim. = stimulus lumineux, Rép. = réponse du sujet au stimulus lumineux, EDG = électrodermogramme (tenir compte des variations EDG dans chaque fragment de tracé, non des valeurs absolues).

300 mg. de Nembutal sont administrés par voie buccale 2 min. avant le début de l'enregistrement; les temps sont indiqués en minutes à partir de cette administration.

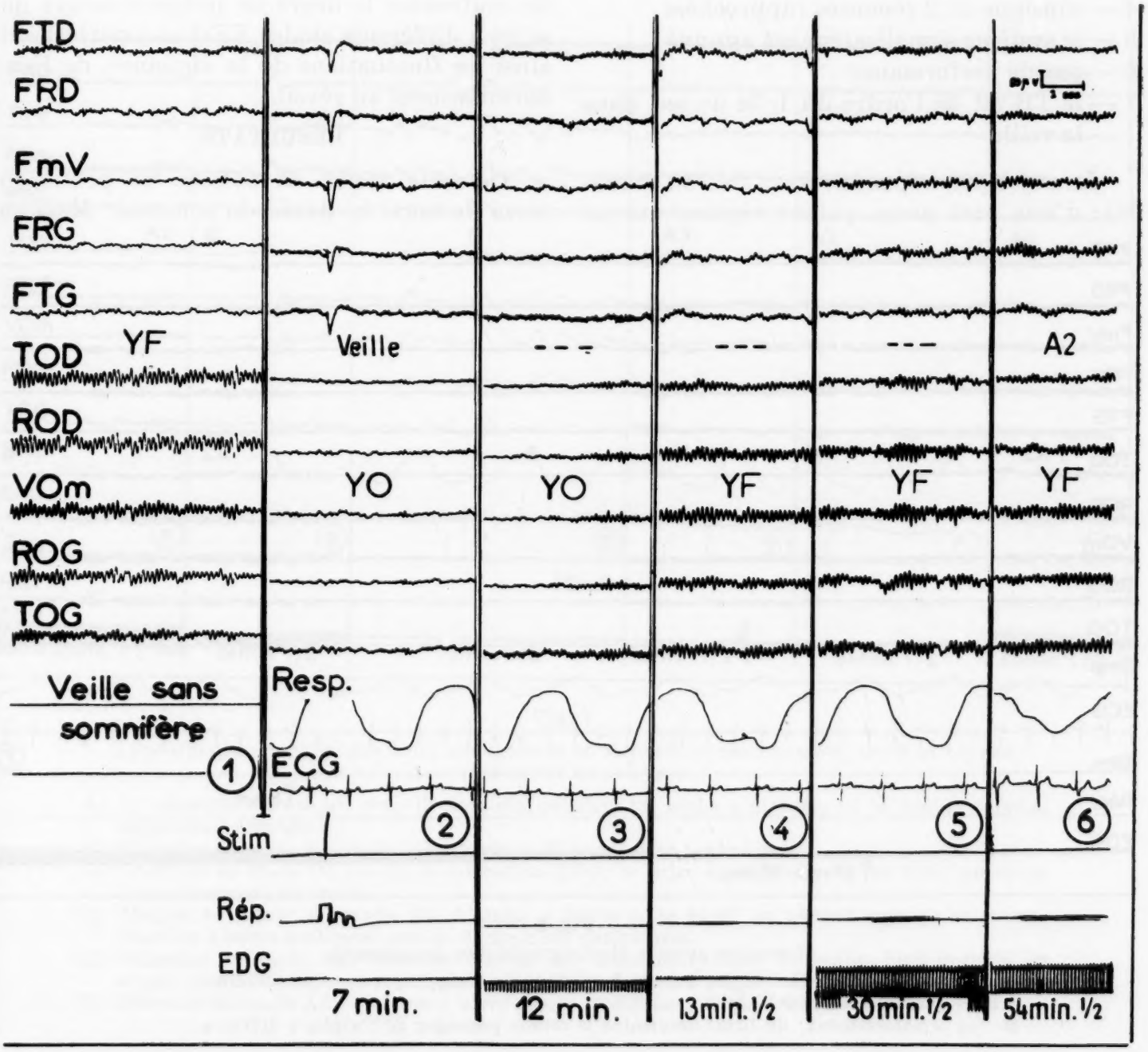

Fig. 1

Veille et endormissement:

1) alpha à l'état de veille les yeux fermés.
2) stimulus et double réponse les yeux ouverts.
3) 4) 5) 6) « diffusion » de l'alpha: apparition progressive d'une activité de même fréquence que l'alpha pariéto-occipital sur la moitié antérieure du scalp.

4 — consigne = une seule réponse
5 — le système signalisateur est lâché
6 — réponse aussi rapide que possible
7 — le TR est de l'ordre du 1/10e de sec.

TR comme « indicateur de l'état de présence »

1 — étudié dans veille ⇄ sommeil
2 — court apprentissage
3 — pas d'avant signal
4 — consigne = 2 réponses rapprochées
5 — le système signalisateur est appuyé
6 — pas de performance
7 — le TR est de l'ordre du 1/5e de sec. dans la veille

Le sujet doit répondre deux fois au stimulus; d'une part parce qu'une réponse unique peut être due au hasard, d'autre part parce que cela permet d'observer des réponses incomplètes. Le TR essentiel est le temps qui sépare le stimulus de la première réponse (TR_1). Pour chaque sujet, les variations de ce TR (évalué en 1/5e de sec.) sont résumées sur un graphique placé en regard d'une courbe schématisant l'aspect EEG à l'instant où le stimulus survient (l'échelle des temps est la même pour ces deux courbes). Le schéma est donc composé de deux courbes « en miroir » avec allongement du TR quand le sujet s'endort, arrêt des réponses quand il dort, réapparition et raccourcissement du TR au réveil (fig. 4 et 7). Les graphiques permettent donc de confronter le degré de présence active du sujet à différents stades EEG et extériorisent ainsi les fluctuations de la vigilance, de l'endormissement au réveil.

RÉSULTATS

De cette façon, on obtient un profil du tracé de toute la durée du sommeil. Mais en dehors de la morphologie EEG du sommeil, de la durée du TR, ou de l'absence de réponse au stimulus, il faut envisager: *a*) le comportement somatique du sujet (yeux fermés, tête penchée, ronflements); *b*) le comportement végétatif (ralentissement cardio-respiratoire,

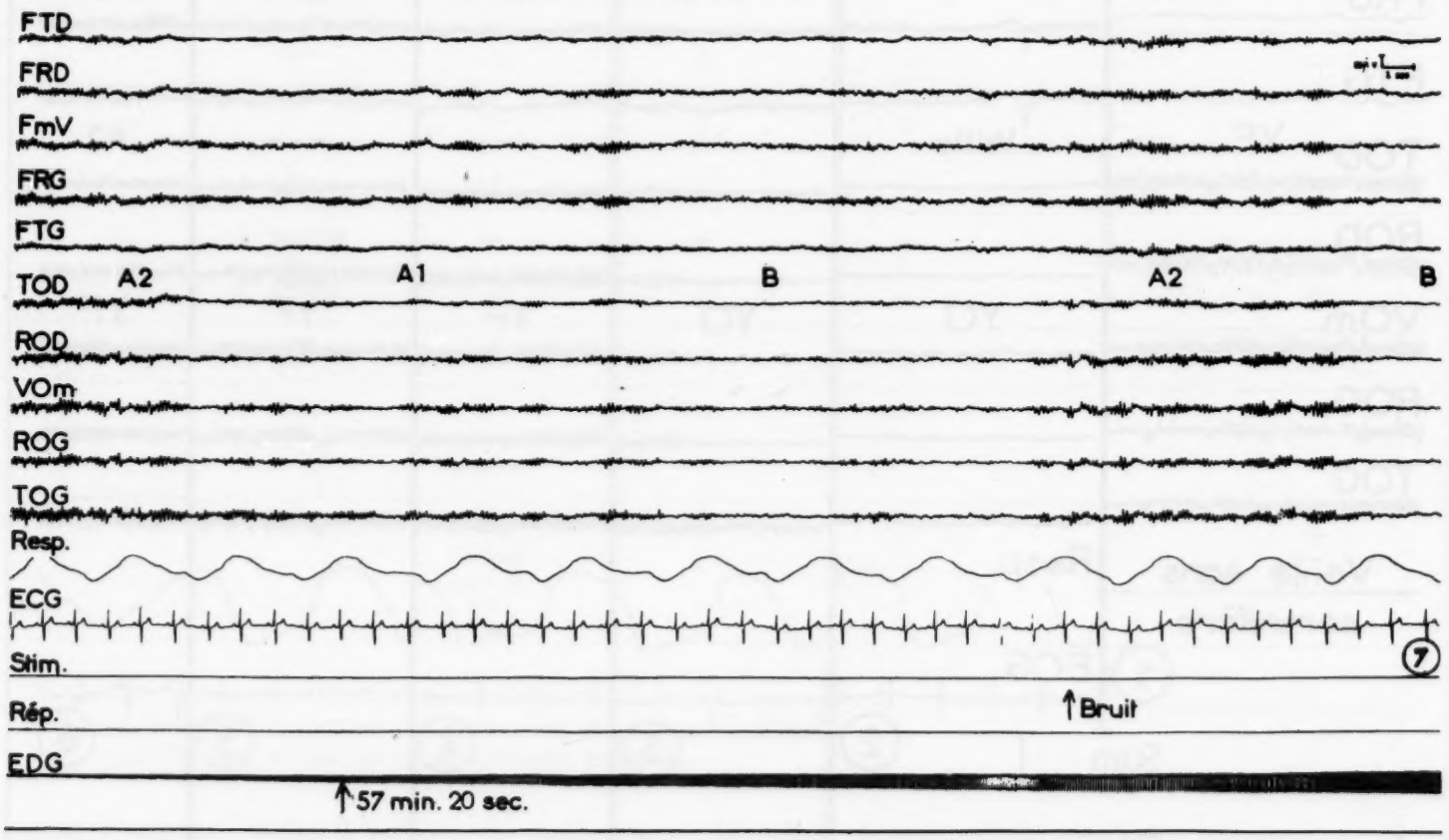

Fig. 2

Premiers aspects électrographiques du sommeil:

7) A2 = « diffusion » de l'alpha à toute la surface du scalp,
A1 = morcellement de l'alpha,
B = aplatissement; un bruit détermine le retour passager de l'alpha « diffus ».

augmentation de la RC) ; *c*) l'appréciation subjective du malade lui-même sur son comportement au cours de l'examen (veille — sommeil, perception des stimuli, réponses).

Le tableau I résume tous ces facteurs et permet d'individualiser dans les 16 tracés étudiés plusieurs types de sommeil :

II — Un sommeil avec concordance de ces mêmes facteurs, mais le sujet nie avoir dormi.

III — Un sommeil complet du point de vue EEG, somatique et végétatif, au cours duquel le sujet conserve la possibilité de répondre au stimulus, se réveillant un bref moment pour répondre et retombant tout de suite

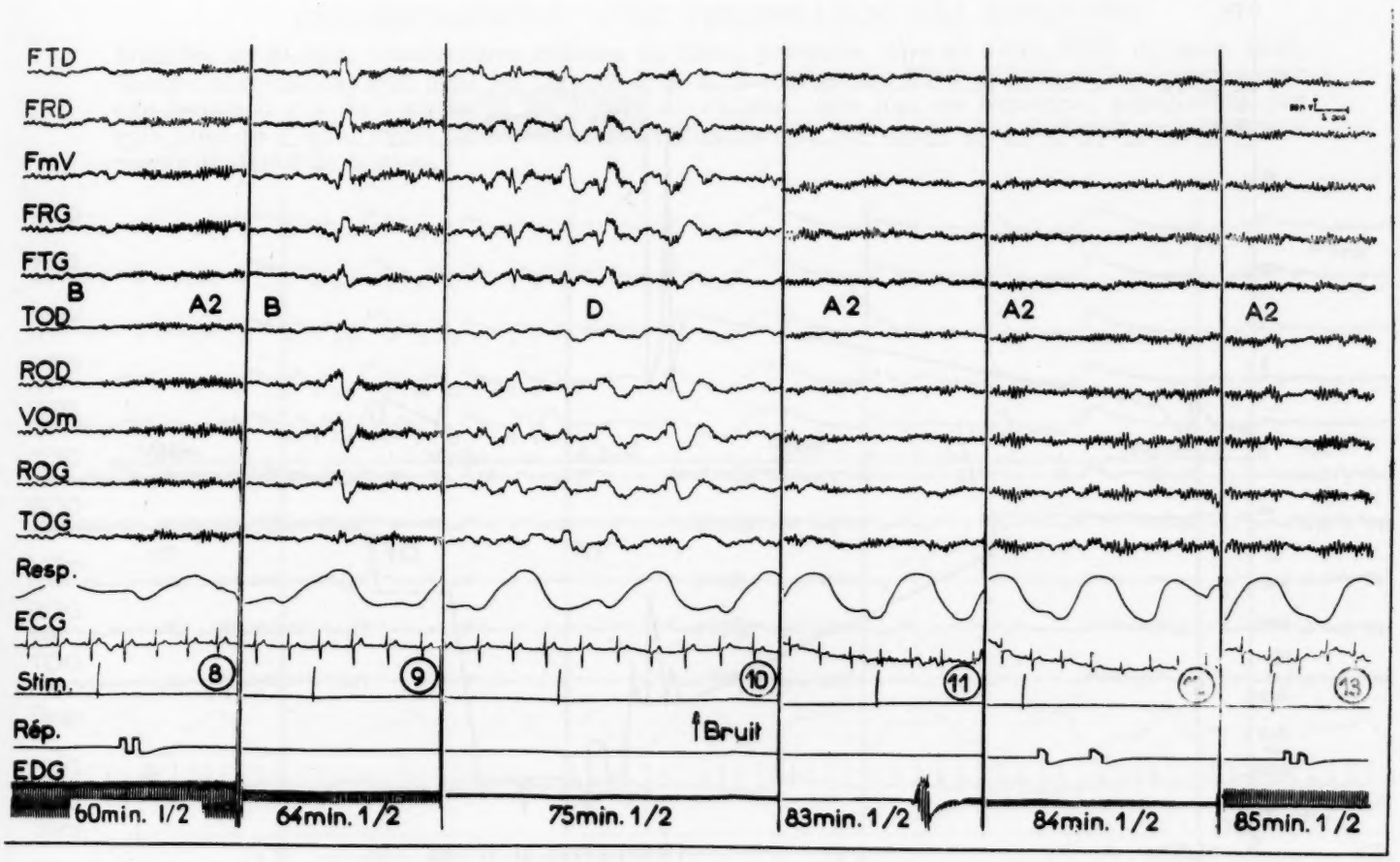

Fig. 3

Approfondissement du sommeil; allongement et disparition des réponses; arrêt et reprise de l'émetteur de présence.

8) Le stimulus envoyé au stade B fait réapparaître un alpha « diffus » et la double réponse légèrement retardée.
9) Stimulus au stade B: suscite un complexe K, le sujet ne répond pas.
10) Stimulus au stade D: pas de modification EEG; le sujet ne répond pas; un bruit provoque l'aplatissement du tracé.
11) Malgré le retour au stade A2 d'alpha « diffus », le sujet ne répond pas au stimulus; réaction d'arrêt seulement sur les dérivations antérieures.
12) Stimulus au stade A2: réaction d'arrêt sur toute la surface du scalp, plus durable en avant; deuxième réponse retardée.
13) Stimulus au stade A2: réaction d'arrêt courte et diffuse; double réponse correcte.

I — Trois sommeils au cours desquels tous les facteurs concordent (signes EEG et aspect somatique de sommeil, ralentissement cardio-respiratoire et augmentation de la RC, ralentissement et disparition des réponses aux stimuli, souvenir du sommeil) (fig. 1, 2, 3, 4).

IV — Deux cas dans lesquels la première partie de l'examen présente des facteurs concordants de sommeil, la deuxième partie un « sommeil » discordant. En effet, dans cette

seconde partie, bien que l'EEG soit au stade A2 peu volté (qui n'est pas du vrai sommeil) les sujets présentent des aspects somatiques et végétatifs de sommeil et ne répondent pas aux stimuli. A l'interrogatoire, ils précisent avoir répondu aux stimuli perçus.

V — Un cas encore plus discordant: EEG au stade A2, absence de réponses aux stimuli, comportement somatique de sommeil, comportement végétatif de veille mais appréciation complexe de l'examen par le sujet lui-même, pendant toute la durée du tracé, il prétend en effet avoir perçu les stimuli mais s'être senti incapable d'y répondre.

VI — Deux sommeils très brefs et légers.

VII — Deux sommeils avec figures électriques pathologiques surajoutées.

VIII — Quatre cas où malgré des conditions d'examens identiques aux précédentes, les sujets ne dorment pas et présentent un comportement concordant de veille.

DISCUSSION

Il se dégage des diverses modalités de sommeil décrites et surtout des discordances signalées qu'il existe plusieurs termes d'appréciation du sommeil:

1) *Appréciation du sommeil par l'EEG.*

Les auteurs cités ont apporté des notions devenues classiques de stades EEG de sommeil (A, B, C, D, E), de réactivité EEG dans le sommeil (retour de l'alpha, potentiels V,

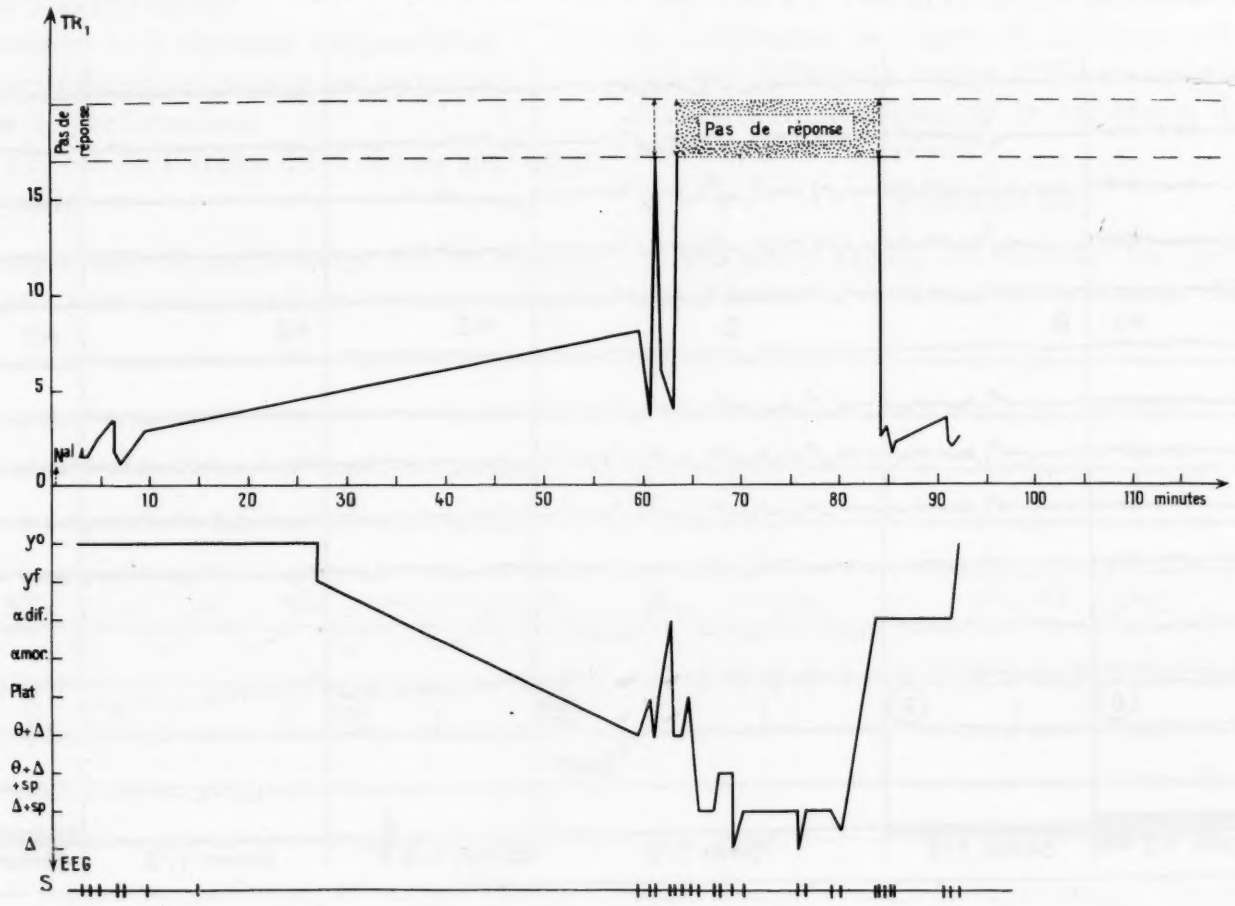

Fig. 4

Courbes en miroir.

Courbe du haut: variations des réponses aux stimuli; allongement du temps de réaction jusqu'à l'arrêt des réponses.
Courbe du bas: stades EEG de sommeil correspondant aux variations ou à la cessation des réponses; la réactivité EEG ne figure pas sur cette courbe.
Les stimuli sont indiqués par les traits verticaux de la ligne S.
TR_1 = temps de réaction en 1/5° de sec. (temps séparant le stimulus du premier élément de la double réponse).
Nal = administration du Nembutal.
α dif. = alpha « diffus », α mor. = alpha morcellé, sp = « spindles », θ = theta, △ = delta.

complexes K plus ou moins dégradés) ; ils ont rattaché le début du sommeil vrai au stade C des « spindles » rolandiques.

Il nous est cependant apparu dans l'étude de l'endormissement et du réveil que l'on pouvait décrire un stade intermédiaire entre le stade A de veille et le stade B d'aplatissement global. Réservant le terme A1 au morcellement de l'alpha, nous appelons A2 le stade d'« activité alpha diffuse ».[1] Cette diffusion en avant d'une activité alpha peut précéder le morcellement de l'alpha, succéder insensiblement aux potentiels rapides du complexe K ou survenir comme réaction d'éveil faisant partie du « retour » de l'alpha. Ce stade n'est pas passé inaperçu des auteurs américains et il faut noter que ses éléments ne doivent pas être confondus avec le rythme proche de 10 c/sec. qui surcharge les grandes ondes lentes du sommeil au stade D et qui est habituellement rapproché des « spindles ». S'il est difficile pour le moment d'affirmer que l'activité alpha diffuse puisse atteindre les régions frontales, il est certain qu'elle atteint les régions prérolandiques et temporales antérieures. Le

Observation II (figures 5, 6 et 7)

ENDORMISSEMENT AVEC PERSISTANCE DES RÉPONSES

Malades de 24 ans; traumatisme crânien en 1952; première crise en 1953, EEG de mars 1957. Mêmes abréviations que pour les figures 1, 2, 3. Les réponses EDG aux stimuli n'apparaissent que lorsqu'il y a de l'alpha ou un retour de l'alpha. 300 mg. de Nembutal administrés par voie buccale 7 min. après le début de l'enregistrement; les temps sont indiqués en minutes à partir du début de celui-ci.

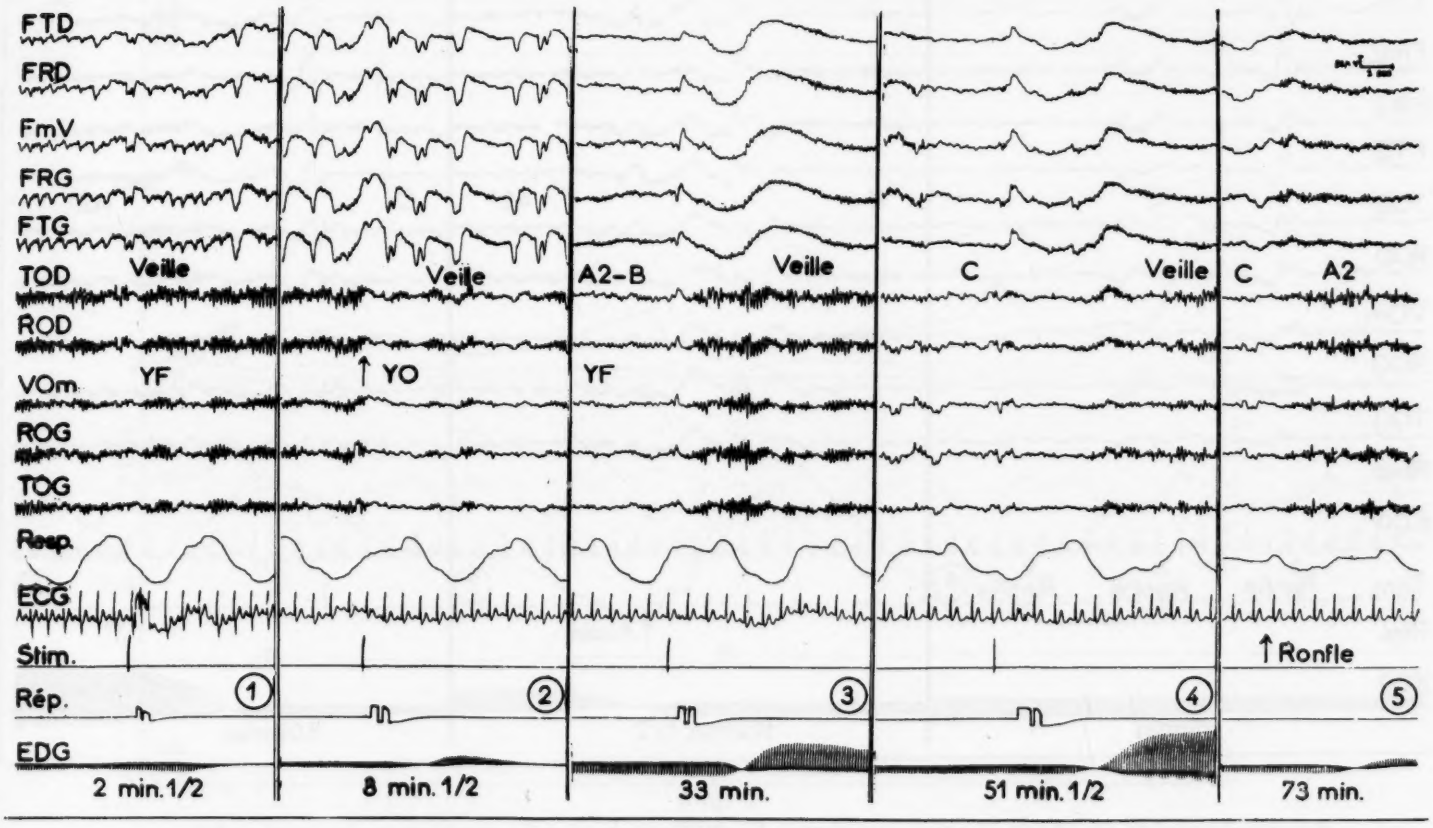

Fig. 5

Veille, endormissement, sommeil sans perturbation de l'indicateur de l'état de présence.

1) Etat de veille — double réponse correcte au stimulus sans modification EEG.
2) Double réponse correcte avec ouverture des yeux et réaction d'arrêt.
3) Stimulus au stade B: retour de l'alpha pariéto-occipital double réponse correcte.
4) Stimulus au stade C: « potentiel évoqué », suivi après quelques secondes d'un retour de l'alpha; double réponse à peine retardée.
5) Ronflement au stade C déterminant l'apparition d'un alpha « diffus ».

[1] « Alpha diffus » ne préjuge pas dans ce travail de la signification physiologique de ce rythme mais de la large répartition sur le scalp d'une activité de morphologie et de fréquence comparable à l'alpha occipital de veille.

Nembutal favorise peut-être cette diffusion mais il ne semble pas qu'il en soit entièrement responsable. Un aspect identique d'extension du rythme alpha d'arrière en avant se retrouve en effet dans plusieurs circonstances: somnolence survenant pendant l'hyperpnée ou la stimulation photique, au moment de l'endormissement et surtout du réveil dans la narcolepsie.

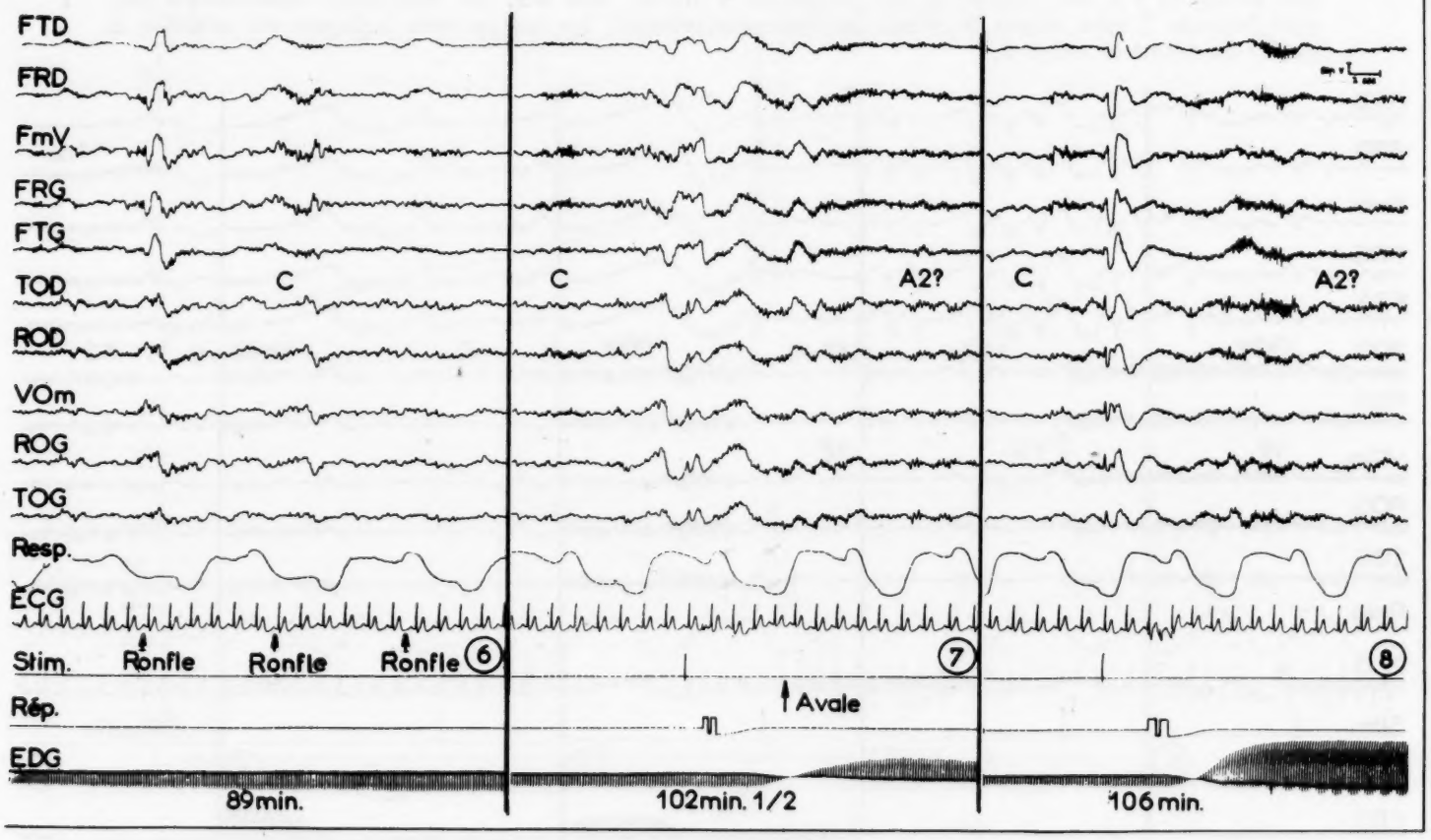

Fig. 6

6) Ronflements au stade C avec complexes K se dégradant à la répétition du « stimulus ».
7) Stimulus au stade C, coïncidant avec un complexe K spontané: retour de l'alpha diffus, double réponse correcte.
8) Stimulus au stade C: potentiel évoqué et complexe K provoqué suivi de retour de l'alpha « diffus », double réponse présente mais retardée.

2) *Appréciation du sommeil grâce à l'indicateur de l'état de présence.*

Au premier abord, il semble que lorsque les réponses aux stimuli suivent la séquence réponse correcte, réponse allongée, absence de réponse, réponse allongée, réponse correcte on puisse parler de variations de vigilance allant de la veille à l'endormissement, au sommeil, au réveil et de nouveau à la veille. Cependant, pour que ceci soit vrai, il faut que les facteurs nécessaires à une réponse correcte soient rassemblés. Ce sont: la compréhension et le souvenir de la consigne, la perception du stimulus, la volonté de répondre, la possibilité d'exécution motrice de cette réponse. Or dans les divers types de sommeils énumérés plus haut on a vu combien chacun de ces facteurs entrant en jeu, le schématisme des concordances peut se trouver modifié.

3) *Appréciation du sommeil par le sujet lui-même.*

L'interrogatoire du sujet après réveil apporte des renseignements précieux mais quelquefois déconcertants. Car, s'il semble banal de nier les signaux qui n'ont pas été perçus, la négation du sommeil malgré des signes EEG de sommeil profond et des ronflements retentissants soulève l'important problème de l'amnésie du sommeil. Ce problème a déjà été en-

visagé dans les travaux de Kleitman (1939) et de Blake et collab. (1939). Le contrôle des communications enregistrées grâce à l'indicateur de l'état de présence est dans ces cas d'un grand secours et constitue une « mémoire » plus sûre que celle du sujet.

Une observation récente du Dr Held, n'appartenant pas à la série du tableau I, est particulièrement significative à cet égard: une malade de 30 ans consulte pour des insomnies rebelles et des images « hypnagogiques » agaçantes. Après administration de 300 mg. de Nembutal elle dort électriquement et cliniquement (chute du tonus, ronflements bruyants, ralentissement cardiaque, arrêt des réponses aux stimuli lumineux) ; mais au réveil, elle nie catégoriquement avoir dormi, affirme s'être simplement sentie étourdie et avoir été consciente pendant tout l'enregistrement. Sans le contrôle du TR, sans l'affirmation, de toute évidence inexacte, de la malade d'avoir répondu à tous les stimuli, on aurait pu envisager l'élaboration d'une théorie sur les figures EEG de sommeil sans véritable sommeil...

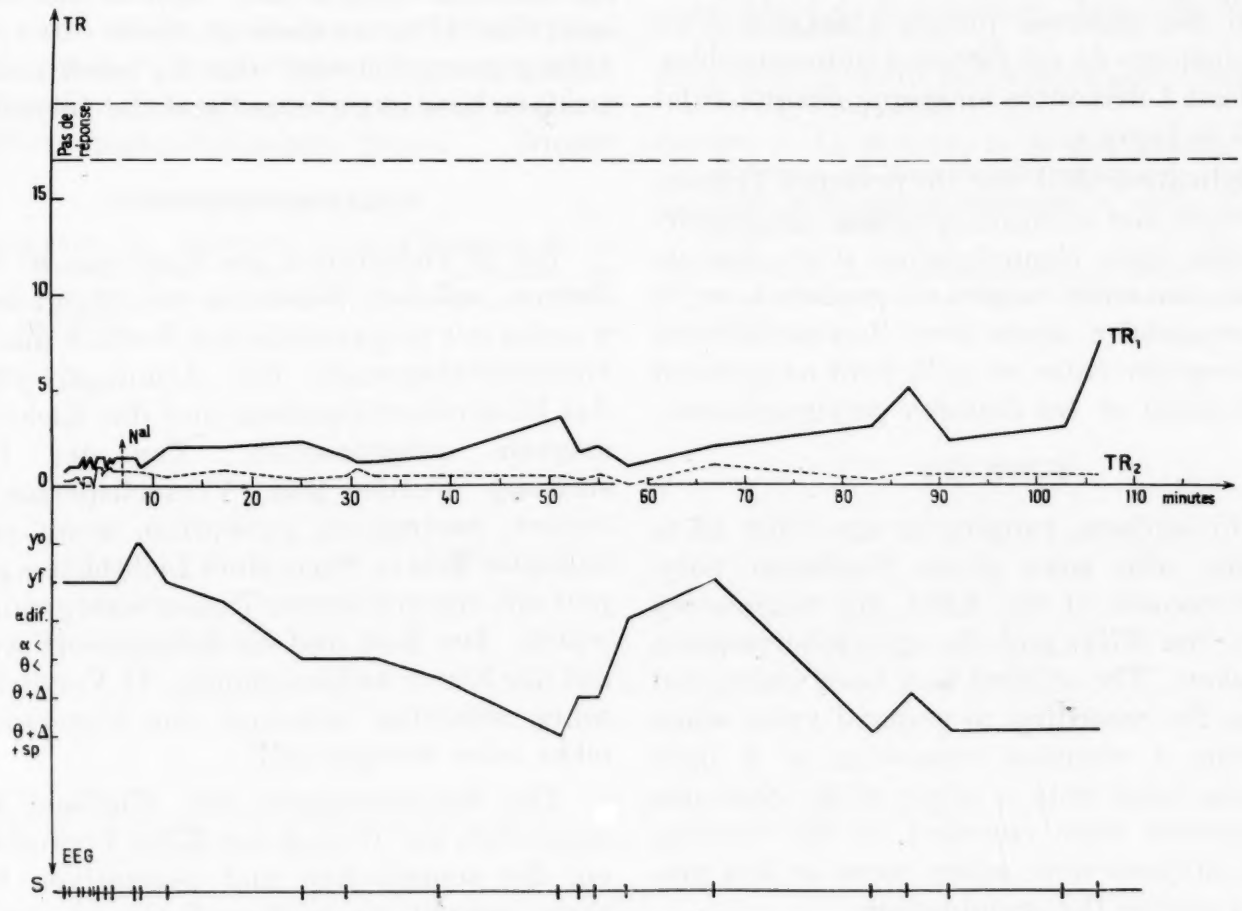

Fig. 7

Courbes en miroir: même réalisation que celle de la figure 4.

Même abréviations que pour la figure 4: TR = temps de réaction en 1/5° de sec., TR_1 = temps séparant le stimulus lumineux du premier élément de la double réponse, TR_2 = temps séparant les deux éléments de la double réponse, $\alpha <$ = alpha très peu volté, $\theta <$ = théta très peu volté.

CONCLUSIONS ET RÉSUMÉ

Quinze sujets âgés de 10 à 55 ans sont enregistrés, après absorption de Nembutal, par une technique polygraphique: EEG, rythme respiratoire, électrocardiogramme, électrodermogramme; l'instruction leur est préalablement donnée de répondre deux fois quand ils perçoivent un stimulus (« flash » lumineux associé à un léger clic) ; stimuli et réponses s'inscrivent sur le tracé. Onze sujets ont dormi d'un sommeil plus ou moins profond.

Les fluctuations de la vigilance s'expriment en termes EEG, somato-végétatifs ainsi

que par la persistance, la détérioration ou la disparition des communications sujet/observateur. L'étude du tableau I (3ème et 4ème colonnes) souligne l'existence de deux catégories de sujets : ceux qui malgré des signes EEG de sommeil conservent le contact avec l'observateur (III et VI), ceux qui au contraire perdent ce contact (cas I, II, IV, V, VII). La réponse correcte au stimulus atteste le souvenir de la consigne, la perception du stimulus, la possibilité motrice du sujet ; la disparition des réponses prouve l'absence d'un ou de plusieurs de ces facteurs indispensables. Le tableau I démontre ainsi que chaque sujet dort « à sa façon ».

L'indicateur de l'état de présence (réponses du sujet aux stimuli) constitue un complément utile dans l'appréciation d'un état de sommeil ; car aussi coopérant que soit le sujet à l'interrogatoire, après réveil il existe souvent une divergence entre ce qu'il croit ou prétend avoir ressenti et les données polygraphiques.

SUMMARY

In 15 subjects, ranging in age from 10 to 55 years, who were given Nembutal polygraphic records of the EEG, the respiratory rhythm, the EKG and the electrodermogram were taken. The subject had been instructed prior to the recording to respond twice when perceiving a stimulus consisting of a light flash associated with a slight click. Stimulus and response were recorded on the tracing. Eleven subjects were asleep more or less profoundly during the examination.

The fluctuations of vigilance expressed themselves in electroencephalographic and somato-autonomic signs as well as by the persistence, the deterioration or the disappearance of the rapport between the subject and the observer. A study of table I (3rd and 4th column) demonstrates that the subjects were falling into two categories: those which, although showing EEG signs of sleep, preserved the possibility of contact with the observer (cases III and VI,) and those which on the contrary lost this contact (cases I, II, IV, V and VII). A correct response to the stimulus indicated that the subject had remembered his instructions, that the stimulus had been perceived and that the subject was capable of a motor response. The disappearance of the response proves the absence of one of these required factors for responding. Table I demonstrates that each subject sleeps "in his own manner".

The indicator of the state of responsiveness (the subject's response to the stimuli) constitutes a useful complementary method to appreciate the state of sleep, for however cooperative a subject may appear during an interview after awakening, there often exists a discrepancy between what he believes or pretends to have experienced and the polygraphic record.

ZUSAMMENFASSUNG

Bei 20 Individuen im Alter von 10 bis 55 Jahren, welchen Nembutal verabfolgt wurde, wurden mit polygraphischer Technik das Elektroenzephalogramm, der Atmungsrhythmus, das Elektrokardiogramm und das Elektrodermogram aufgenommen. Vor der Untersuchung wurde jede Versuchsperson instruiert, zweimal zu antworten, wenn ein bestimmter Reiz in Form eines Lichtblitzes gekoppelt mit einem leichten Ticken wahrgenommen wurde. Der Reiz und die Reizantwort wurden auf der Kurve aufgenommen. 11 Versuchspersonen schliefen während der Untersuchung mehr oder weniger tief.

Die Schwankungen der Vigilanz waren ersichtlich auf Grund der EEG-Veränderungen, der somatischen und vegetativen Symptome, sowohl als auch auf Grund der Persistenz, der Verschlechterung oder des Verschwindens des Rapportes zwischen Versuchsperson und Beobachter. Aus Tafel I (3. und 4. Kolonne) wird ersichtlich, dass die Versuchspersonen sich in zwei Kategorien verteilen : Diejenigen, welche trotz elektroencephalographischen Zeichen des Schlafes den Kontakt mit dem Beobachter beibehalten (Fälle III und VI) und diejeningen, welche im Gegensatz dazu diesen Kontakt verlieren (Fälle I, II, IV, V und VII). Eine korrekte Reizantwort bezeugt das Erinnerungsvermögen für die Instruktion, die der Versuchsperson gegeben worden war, die Wahrnehmung des Reizes und das motorische Reak-

tionsvermögen der Versuchsperson. Das Verschwinden der Reizantworten bezeugt das Fehlen eines dieser drei unerlässlichen Faktoren. Tafel I zeigt daher, dass jedes Individuum "nach seiner Fasson" schläft.

Der Indikator für das Antwortvermögen (Reizantwort der Versuchsperson) erweist sich daher als ein nützliches Hilfsmittel, um den Schlafzustand zu messen. Wie sehr eine Versuchsperson auch bereit sein mag, auf Fragen nach dem Aufwachen Antwort zu geben, so existiert doch eine Diskrepanz zwischen dem, was die Versuchsperson glaubt oder behauptet empfunden zu haben, und den objektiven polygraphischen Daten.

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THE EEG JOURNAL

STUDIES ON THE FLAT ELECTROENCEPHALOGRAM IN MAN

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(Received for publication: September 21, 1957)

The following report deals with the "flat EEG" in healthy subjects and in neurological and psychiatric patients. The observations are mostly based on flat EEG's of unknown cause. As a supplement to this, some cases with transitional flattening after head injuries are described.

Flat EEG's are quite well known and often mentioned in the literature. According to recent estimates their incidence is about 10 to 15 per cent in healthy persons (Jung 1953; Meyer-Mickeleit 1953). In these estimates special conditions such as advanced age, fatigue, drowsiness, sleep (Gibbs and Gibbs 1950) and anaesthesia (Beecher and McDonough 1938; Denny-Brown 1947) are taken into consideration, as these conditions may cause transitory flattening of the EEG in certain cases. Already in 1940 Jasper *et al.* mentioned that a flat EEG could occur as a long time sequel after brain injuries and more recently this has been confirmed by others (Harvey and Rasmussen 1951; Fois *et al.* 1955). The somewhat different interpretations are probably due to differences in nomenclature and to statistically insufficient data. Therefore, it appeared useful to study the occurrence and distribution of flat EEG's according to age and diagnosis in a considerable number of neurological and psychiatric patients as well as in healthy subjects.

We use the term "flat" for EEG's which do not show spontaneous activity of higher voltage than 20 μV. The majority of these EEG's consist of irregular activity of varying frequencies which merge into each other and do not show any constant frequencies even during hyperventilation. In rare cases there is almost no spontaneous activity at all. The flat EEG is, therefore, according to our nomenclature, fundamentally a low voltage, fluctuating frequency EEG.

MATERIAL AND METHODS

A group of 427 patients without neurological or psychiatric disorders and with normal EEG's served as a control group; 283 were male, 144 female. The age varied between 12 and 64 years. The majority of these patients had been referred to us by general practitioners and by clinics of other specialisms. The type of disorder for which they were referred and the normal neurological, radiological and EEG findings made participation of cerebral factors unlikely. In the selection of patients we have endeavoured to obtain a uniform distribution in the various age-groups (table I).

TABLE I

The flat EEG in 427 healthy persons without neurological or psychiatric disorders

	Age			Summa
	10-19	20-39	40-69	
Number of EEGs	77	164	186	427
flat EEGs	1	12	20	33
% flat EEGs	1%	7%	11%	8%
3 σ	0.2-10%	3.3-16.2%	2.8-19.4%	4.5-12.3%

TABLE II

The flat EEG in 2000 neurological and psychiatric patients

Clinical diagnosis	Age			Number of EEGs — n —	% n flat	χ^2
	1-19	20-39	40-69	flat: — fl—		
Idiopathic epilepsy	118	123	110	n = 451		
				fl = 0		
Symptomatic epilepsy	111	92	11	n = 214		
				fl = 0		
Heredodegenerative syndroms and infantile brain diseases	39	18		n = 57	7	0.3
	1	3		fl = 4		
Encephalitis	14	21	4	n = 39	5	0.3
		1	1	fl = 2		
Closed head injuries	71	377	84	n = 532	6	1.0
	2	22	8	fl = 32		
Brain tumors	8	61	44	n = 113	6	0.7
		4	3	fl = 7		
Encephalatrophy		2	38	n = 40	12	1.5
		1	4	fl = 5		
Cerebral vascular diseases		25	287	n = 312	13	6.0 $0.01 < p < 0.05$
		2	39	fl = 41		
Endocrinopathy	7	13	8	n = 28	18	3.6 $p \sim 0.05$
		1	4	fl = 5		
Schizophrenia and cyclothymia	38	121	18	n = 177	9	0.9
	2	11	2	fl = 15		
Psychopathy and neurosis	2	21	14	n = 37	19	1.5
		2	5	fl = 7		
Summa	178	659	497		6	
	5	47	66			
% flat	3%	7%	13%			

The group of 2000 neurological and psychiatric patients consisted in patients of both sexes, mainly between the ages of 18 and 67 years (table II).

All cases in which the diagnosis was uncertain and 168 patients of whom more than one EEG had been recorded were left out. Transitory flattening due to drowsiness, fatigue and arousal and post-ictal low-voltage records were not taken into account. Five patients with EEG flattening after a head injury were also eliminated; they will be discussed separately (fig. 3).

TABLE III

"Flat" and "low voltage α — EEG" of healthy persons in hyperventilation.

	33 flat EEGs	50 low voltage α — EEGs
Obvious activation	—	38
Insignificant	18 (increase of 14-30 c/sec. and muscle)	12

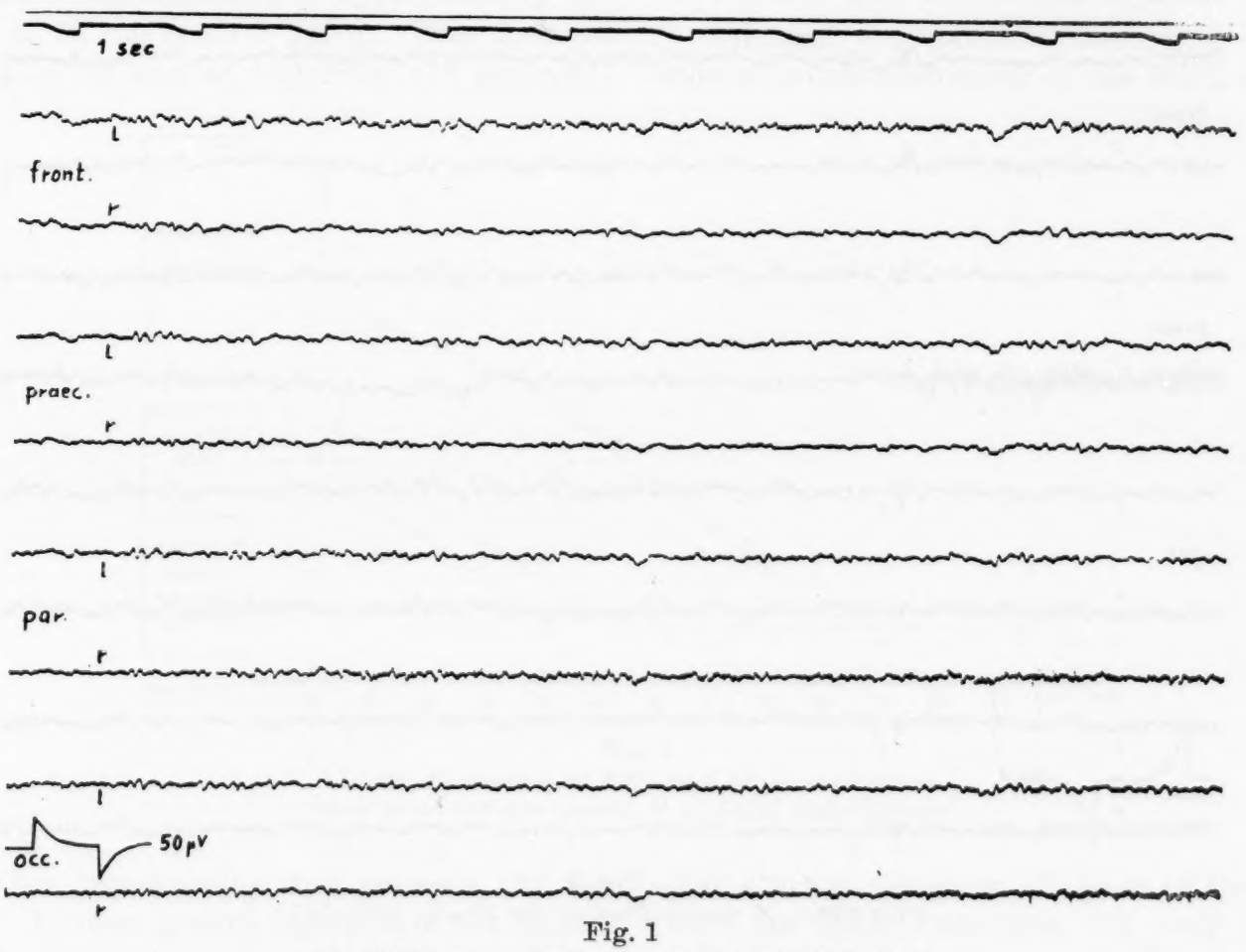

Fig. 1
Flat EEG. 7 mm. deflection for 50 μV. (783/58).

In 33 of the 151 cases with flat EEG's hyperventilation was carried out. The EEG's were recorded on 4- or 8-channel Schwarzer electroencephalographs. The standard electrodes placement consisted of 10 electrodes corresponding to the frontal precentral, parietal and occipital regions of the brain. Chiefly the common reference method was used: electrodes on the earlobes as a reference. The bipolar method was also used.

RESULTS

The pattern of the flat EEG.

The flat EEG is easily recognized with the usual amplifications (7 mm. deflection for 50 μV., fig. 1) or 18 mm./50 μV. (fig. 2). It is characterized by a few small waves of varying frequencies with amplitudes up to 20 μV. No dominant frequency can be recognized in this type of EEG. Usually there is a mixture of waves with frequencies ranging between 7

and 35 per sec. The frequencies lower than 7 per sec. usually can not be differentiated from movement artefacts and fluctuations of the baseline. The frequencies higher than 30 per sec. cannot be differentiated from muscle potentials. There is mostly only very little blocking on opening of the eyes. Hyperventilation often leads to an increased activity of 14-25 per sec. Generally hyperventilation does not produce any marked activation leading to useful additional information. As a rule one can distinguish from this type of EEG the low voltage alpha EEG, with more constant frequencies and changing during hyperventilation. Only very rarely an almost completely flat EEG occurs in patients with unclouded consciousness — hardly ever in otherwise normal subjects.

In 12 persons 2 EEG's were recorded with intervals varying between 10 days and 9 months. Within this period the electrical patterns remained constant. The flat EEG, therefore, appears to be a feature of long duration. The obviously shorter, transitory flattening of the EEG immediately following brain contusions (fig. 3) is an exception to this.

The flat EEG in patients without neurological or mental disorders.

We can regard these patients as a control group (table I). In all age groups taken together the incidence of flat EEG's was 8 per cent. With advancing age, however, the flat EEG becomes more frequent. It was most frequent in patients between 40 and 69 years (11 per cent). The differences in this table are statistically significant.

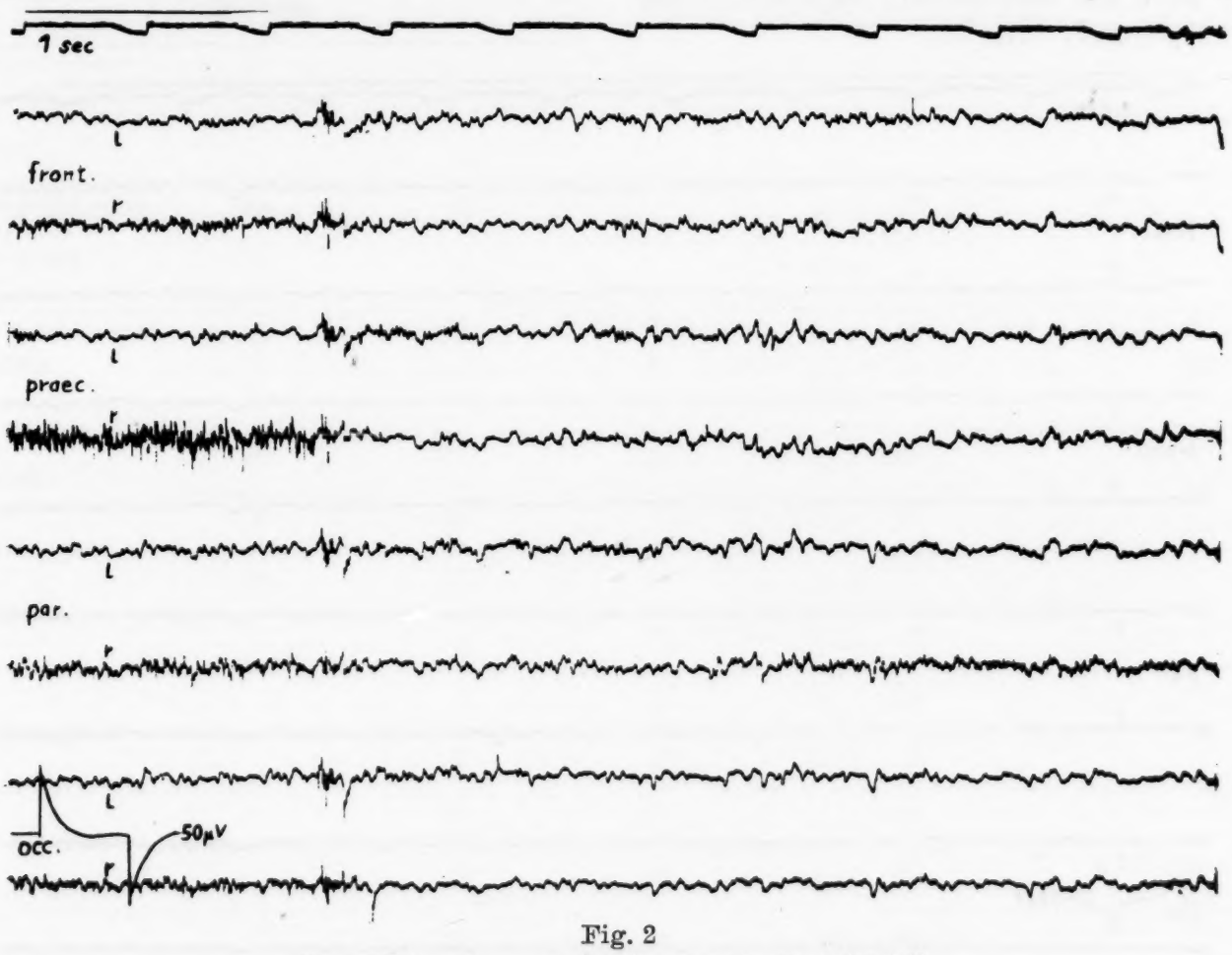

Fig. 2
Flat EEG. 18 mm. deflection for 50 μV. (783/58).

The flat EEG in neurological and psychiatric patients.

The age distribution of these patients is not uniform, because they were selected according to diagnostic groups. A particularly striking feature was revealed in the group of

epileptic patients: in idiopathic as well as in symptomatic epilepsy there were no flat EEG's. This is remarkable because epileptics, together with patients with closed head injuries and cerebral vascular disorders are particularly well represented. In the groups of patients with cerebral vascular diseases and cerebral atrophy there appear at first sight to be more flat EEG's than in the control group: 13 per cent and 12 per cent respectively. However, if the age of onset of the disease is taken into account (between the age of 40 and 70), the incidence is approximately the same as in the control group. This does not obtain in the case of endocrine (18 per cent) disorders, psychopathy and neurosis (19 per cent). In these groups the onset of the disease usually lies between 20 and 40 years. Therefore, the percentages clearly exceed those of the control groups (table I). Most of the flat EEG's were found in patients without clinically verifiable organic disorders of the brain. In cases with previous cerebral disorders (head injuries, encephalitis, infantile cerebral diseases) or actually suffering from brain diseases such as cerebral tumors, we found approximately the same incidence of flat EEG's as in the control groups of the corresponding age.

Just as in the control group flat EEG's occurred more frequently with increasing age in the group of patients of table II. The smaller percentage of flat EEG's particularly in the first half of life is obviously caused by the absence of flat EEG's in the group of 665 epileptic patients. When this group is left out of the total, the proportion of flat EEG's is 9 per cent as compared to 8 per cent for the control group. The differences in the proportion of flat EEG's in the 3 age groups of table II are also statistically significant.

Flat EEG's after closed head injuries.

Amongst our patients there were 5 who showed initial flattening of the EEG shortly after a brain contusion. In each of these patients the EEG flattening was only temporarily evident at most up to the 17th day after the trauma.

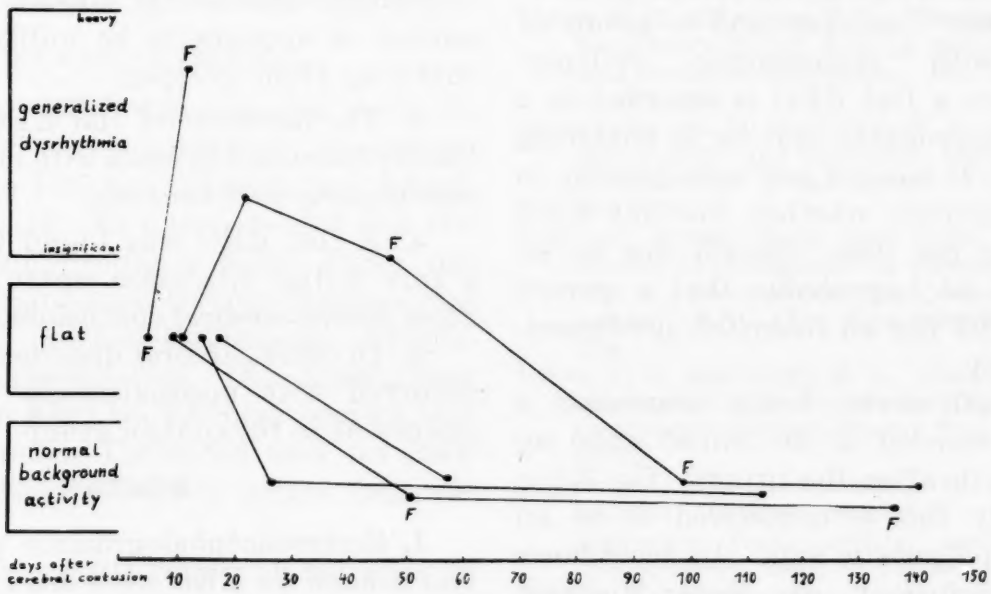

Fig. 3
Initial flattening of EEG in 5 brain contusions
(each point for one record, F = focal disturbances).

DISCUSSION

The flat EEG has been defined as an EEG of low voltage and with varying frequencies. This definition is based on 2 simple criteria and embraces a characteristic type of EEG. The flat EEG, therefore, must be distinguished from the EEG with a definite α rhythm of low amplitude which could be named "low voltage α EEG". The flat EEG is even more

characterized by the absence of constant frequencies than by the low voltage. In doubtful cases hyperventilation may help to classify the EEG: in the flat EEG even with increased amplitude there is no constant dominant frequency, whilst in the low voltage α type of EEG the α rhythm usually becomes more prominent.

According to Cress and Gibbs (1948) at least a limited activation of the low voltage EEG can occur during sleep. We are not able to report details, since we have too few EEG's recorded during sleep at our disposal.

The flat EEG as defined in the present study occurs in approximately 10 per cent of all adults. It is therefore striking that no flat EEG's were found, in a group of 451 patients with ''idiopathic'' epilepsy and a group of 214 patients with ''symptomatic'' epilepsy. Therefore, when a flat EEG is recorded in a patient it is improbable that he is suffering from epilepsy. It has not yet been possible to determine accurately whether the flat EEG persists during the time. Should this be so, then it would be improbable that a person with a flat EEG has an inherited predisposition for epilepsy.

In cases with severe brain contusions a flat EEG is recorded in the initial stage up till half a month after the injury (fig. 3).

Occasionally this is considered to be an unfavourable prognostic sign. In accordance with the conclusions of Meyer-Mickeleit (1953) it does not appear to be justified to assume that a patient has had a brain contusion only because of a flat EEG recorded several months or years after a closed head injury.

The increased occurrence of flat EEG's in cases with endocrinopathy, psychopathy and neurosis could either be due to inherited tendencies or be directly caused by these disorders. Our present knowledge of the relationships between electrical activity of the cortex and metabolism is not sufficient to give a satisfactory explanation of these findings.

SUMMARY

The flat EEG has been defined as an EEG of varying frequencies ranging from 7-35 per sec. with amplitudes not higher than 20 μV. It may be distinguished from other low voltage EEG's by the absence of a dominant frequency, and slight uncharacteristic activation with hyperventilation. The evaluation of 163 flat EEG's in a total of 427 patients not suffering from neurological or psychiatric disorders and of 2000 neurological and psychiatric patients has given the following results:

1. Approximately 10 per cent of adults of both sexes without neurological or psychiatric disorders have a flat EEG; the proportion is considerably smaller in childhood. The incidence increases with the age.

2. In 665 patients with idiopathic or symptomatic epilepsy no flat EEG was found. Therefore, when a flat EEG is recorded in a patient it appears to be unlikely that he is suffering from epilepsy.

3. The incidence of flat EEG's was significantly increased in cases with endocrinopathy, psychopathy and neurosis.

4. A flat EEG was found temporarily as a rare initial alteration up to half a month after severe cerebral contusions.

5. In other cerebral disorders the flat EEG occurred with approximately the same frequency as in the control group.

RÉSUMÉ

L'électroencéphalogramme plat a été défini comme un EEG avec des fréquences de 7 à 35 c/sec. et avec une amplitude de 20 ou de moins de 20 μV. On peut le distinguer d'autres EEG de bas voltage par l'absence d'une fréquence dominante, et la présence d'une faible activation non-caractéristique produite par l'hyperventilation. L'évaluation d'un total de 163 EEG plats enregistrés dans un groupe de 427 malades qui ne présentaient ni symptômes neurologiques ni symptômes psychiatriques, et l'enregistrement chez 2.000 malades avec des symptômes neurologiques ou psychiatriques nous a donné les résultats suivants:

1. A peu près 10 pour cent des adultes des deux sexes sans maladies neurologiques ou psychiatriques ont un EEG plat; la proportion est considérablement moins importante parmi les enfants. L'incidence augmente avec l'âge.

2. Parmi 665 malades présentant une épilepsie idiopathique ou symptomatique, on n'a enregistré aucun EEG plat. En conséquence, quand on enregistre chez un malade un EEG plat, il est très peu probable qu'il souffre d'une épilepsie.

3. L'incidence des EEG plats était augmentée d'une façon significative chez des malades atteints d'endocrinopathie, psychopathie ou de névrose.

4. Après une contusion cérébrale grave un EEG plat a été trouvé comme une altération initiale rare et cette altération ne dépassait pas les 15 jours.

5. Dans d'autres malades du système nerveux l'EEG plat se rencontrait avec la même fréquence que dans le groupe de contrôle.

ZUSAMMENFASSUNG

Als flaches EEG bezeichneten wir ein Kurvenbild mit unregelmässigen Frequenzen im Bereiche von 7-35 pro Sekunde und Amplituden unter 20 μV. Es unterscheidet sich von anderen kleinamplitudigen EEG durch das Fehlen eines dominanten Grundrhythmus und durch geringe, uncharakteristische Aktivierung bei Hyperventilation. Die Auswertung von 163 flachen EEG bei 427 neurologisch und psychisch gesunden Patienten und bei 2000 Nerven- oder Geisteskranken zeigte folgende Ergebnisse:

1. Ein flaches EEG fand sich bei etwa 10 Prozent der neurologisch und psychisch gesunden Erwachsenen beiderlei Geschlechts; sein Vorkommen ist in der Kindheit erheblich seltener. Die Häufigkeit wächst mit dem Lebensalter.

2. 665 Patienten mit genuiner oder symptomatischer Epilepsie zeigten keine flachen EEG. Daher dürfte beim Vorliegen eines flachen EEG eine Epilepsie unwahrscheinlich sein.

3. Bei endokrinen Krankheiten, Psychopathie und Neurosen sind die flachen EEG signifikant vermehrt.

4. Vorübergehend kann ein flaches EEG als seltene Initialveränderung bis zu ½ Monat nach schweren Hirnkontusionen vorkommen.

5. Bei anderen cerebralen Krankheitsprozessen finden sich flache EEG in etwa der gleichen Häufigkeit wie bei der Vergleichsgruppe.

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IMPORTANCE DIAGNOSTIQUE DE CERTAINES ACTIVITÉS ÉLECTROENCÉPHALOGRAPHIQUES LATÉRALISÉES, PÉRIODIQUES OU À TENDANCE PÉRIODIQUE AU COURS DES ABCÈS DU CERVEAU

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(Received for publication: March 31, 1958)

INTRODUCTION

Ce travail a été entrepris pour vérifier une impression dégagée au cours de ces dernières années, qui tendait à faire ressortir la très grande fréquence d'anomalies paroxystiques localisées caractérisées par leur mode de survenue périodique ou à tendance périodique dans certains cas de néoformations rapidement expansives, en particulier dans les abcès du cerveau.

HISTORIQUE

Depuis quelques années, en effet, l'attention avait à plusieurs reprises été attirée sur des phénomènes EEG paroxystiques se répétant à intervalles plus ou moins réguliers (Pampiglione et Martin 1953).

Le type de ces activités périodiques est représenté par les anomalies rencontrées dans certaines formes de leucoencéphalites type van Bogaert, Pette Doring ou Dawson (Radermecker 1951). Il s'agit de phénomènes paroxystiques répétés à d'assez longs intervalles (10-20 sec.) caractérisés par la stéréotypie morphologique de chaque décharge: cette stéréotypie, d'autant plus manifeste que les décharges sont elles-mêmes constituées par la succession plus complexe d'amples variations de potentiel, est si frappante et si constante que jointe au mode de survenue périodique elle est considérée (Cobb 1958) comme spécifique de ces formes d'encéphalites subaiguës (fig. 1).

Depuis lors on a remarqué des activités EEG analogues, souvent moins complexes, parfois moins stéréotypées dans leur morphologie, mais toujours individualisées par cette récurrence à intervalles à peu près réguliers (Alajouanine, Lecasble et Rémond 1955) au cours d'encéphalites ou d'encéphaloses diverses (infectieuses, démyélinisantes...).

Plus récemment des décharges périodiques non plus bilatérales et synchrones mais latéralisées ou même focalisées ont été signalées dans certaines affections localisées (Dondey et Lecasble 1957; Dickson 1958).

MATÉRIEL ET MÉTHODE

Nous avons retenu les groupements d'éléments graphiques *paroxystiques* et *latéralisés* (localisés ou focalisés) répétitifs mais non rythmiques, lorsqu'ils réalisent une succession de décharges survenant à des intervalles de temps grossièrement superposables et ceci pendant au moins plusieurs minutes au cours d'un même enregistrement.

Avant de préciser cette proposition il convient de remarquer que cette définition élimine les manifestations EEG bilatérales et synchrones et qu'elle ne tient pas compte des altérations non périodiques éventuellement présentes sur le tracé.

L'élément constitutif de la décharge répétitive est parfois monophasique négatif, le plus souvent polyphasique à phase principale négative, d'une durée variant entre ¼ de sec. et une seconde ou plus et d'amplitude variant généralement entre 50 et 100 μV. Il présente souvent un front raide qui justifie la qualification d'élément paroxystique. Des éléments constitutifs divers peuvent s'associer dans une

décharge réalisant ainsi des groupements très variables d'un tracé à l'autre.

Le mode de groupement de ces éléments constitutifs permet d'apprécier la *stéréotypie* des décharges qui se trouve, par définition, réalisée lorsque ces groupements sont superposables. En fait, nous avons retenu ici des superpositions même grossières dans la mesure où les variations morphologiques au sein d'une décharge respectaient au moins certains éléments graphiques caractérisés.

La durée des intervalles qui séparent ces groupements permet d'apprécier la *périodicité* des décharges qui se trouve, par définition, réalisée lorsque ces intervalles sont superposables. Là encore, nous avons retenu des superpositions même grossières dans la mesure où les variations de durée des intervalles restaient, lors de l'analyse visuelle du tracé, négligeables par rapport à la durée moyenne des intervalles.

L'imprécision des limites de la variabilité de la stéréotypie et de la périodicité amène d'ailleurs à rappeler que ces deux critères, lors de l'analyse du tracé, sont appréhendés, non pas distinctement mais comme des qualités simultanées et dans une certaine mesure complémentaires pour définir le type d'activité électrique étudiée ici.

On distinguera donc des *anomalies périodiques* lorsque les altérations bien stéréotypées se répètent régulièrement toutes les 3, 5 ou 10 sec., tout au long de l'enregistrement en tranchant sur une activité de base peu perturbée et des *anomalies à tendance périodique* lorsque les altérations, peut-être moins bien stéréotypées, se répètent à intervalles plus longs, toutes les 8, 10 ou 15 sec. par exemple, de façon non permanente pendant la durée de l'enregistrement et en s'isolant moins aisément d'un contexte éventuellement altéré (fig. 2A et 2B).

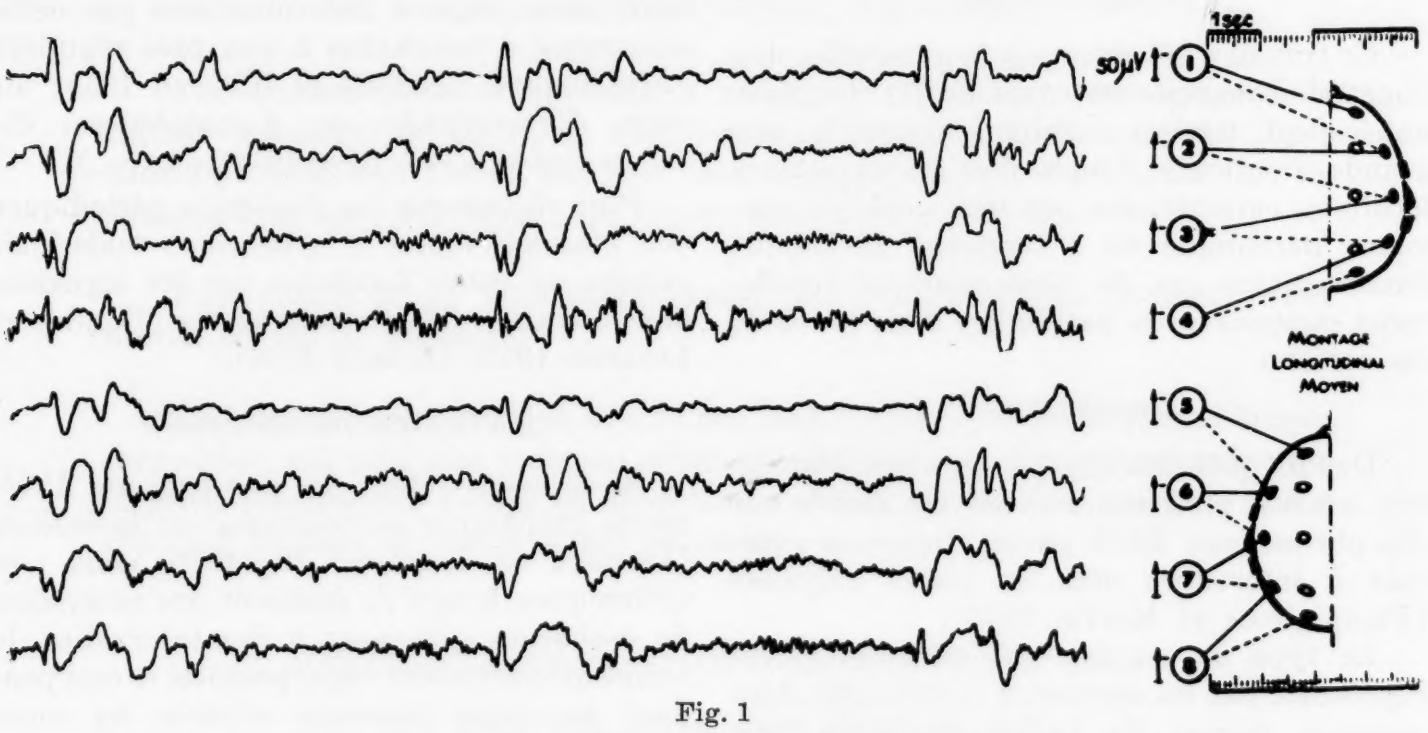

Fig. 1

Montage longitudinal moyen. Décharges périodiques au cours d'une leuco-encéphalite. Noter la périodicité évidente des décharges et la stéréotypie de leur morphologie complexe.

Afin de vérifier la fréquence des anomalies périodiques ou à tendance périodique répondant à l'assez large définition EEG qui vient d'être donnée, nous avons recherché parmi les observations de malades hospitalisés dans le Service entre Décembre 1951 et Décembre 1957 des cas de néoformations rapidement expansives (abcès, hématomes, tumeurs) et pour contrôle nous avons étudié certains processus méningés ou encéphaliques d'origine infectieuse ou vasculaire : soit un total de 120 cas qui comportent tous au moins un EEG

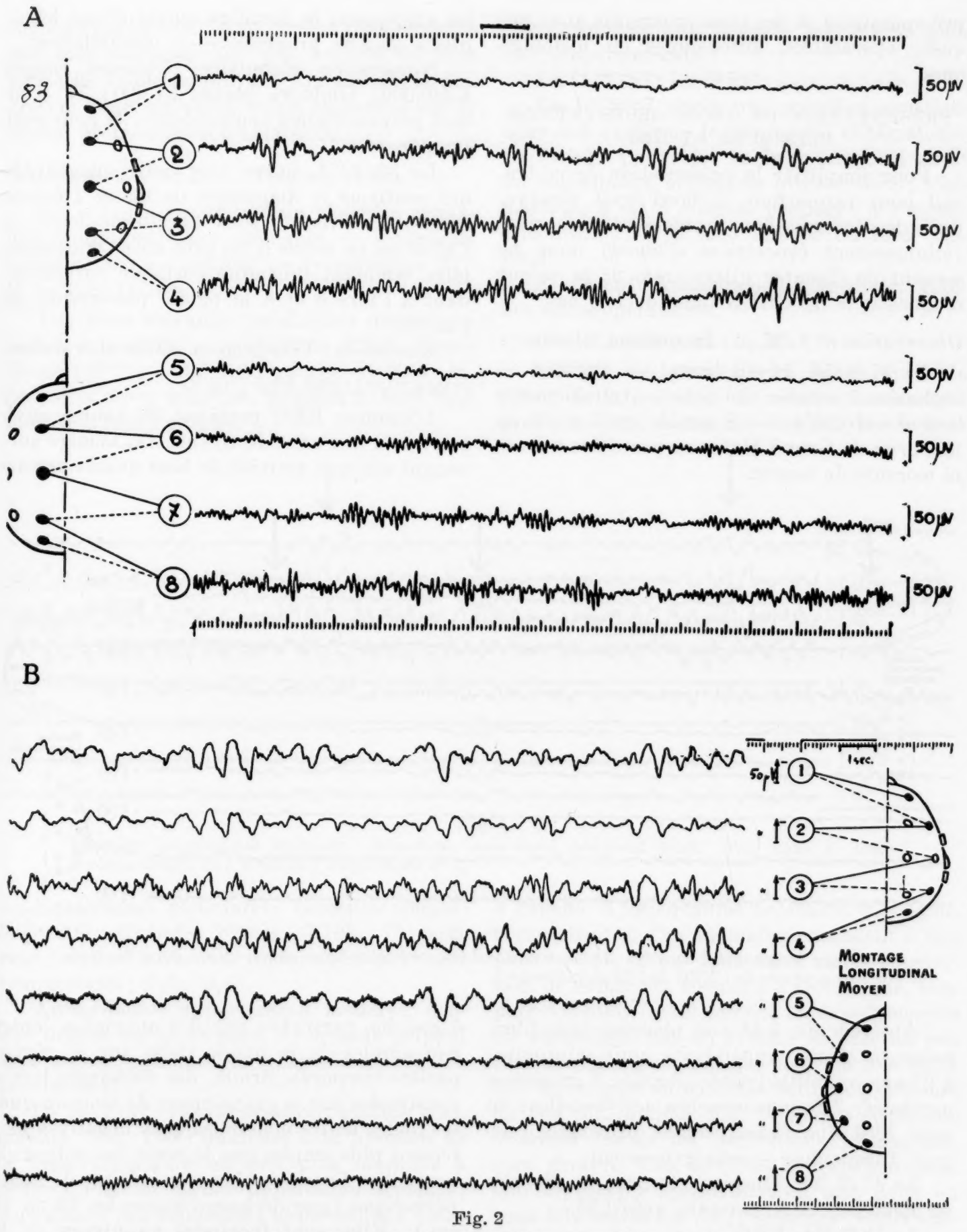

Fig. 2

A. Montage longitudinal supérieur. Décharge localisée (opposition de phases sur la région rolandique haute gauche) de survenue périodique et de morphologie simple.
B. Montage longitudinal moyen. Décharge delta hémisphérique droite, irradiant vers la région frontale gauche différent de la décharge de la figure 2 A par sa localisation, sa stéréotypie et sa périodicité moins nettes.

pré-opératoire et des renseignements anatomiques: opératoires, autopsiques ou histologiques.

PRÉSENTATION DE TROIS OBSERVATIONS CLINIQUES ET EEG

Pour simplifier la présentation de ce travail nous rapportons d'abord trois observations de néoformations rapidement expansives (cliniquement évocatrices d'abcès) nous réservant de discuter ultérieurement la valeur diagnostique de l'EEG dans de tels cas.

Observation nº 1: M. . . . Jacqueline, 31 ans

Le 17/9/54: réveil brutal — angoisse — céphalées frontales violentes — tremblements intenses et diffus — il semble qu'il y ait eu une crise de Grand Mal sans perte des urines, ni morsure de langue.

Antécédents: à 11 ans, pleurésie séro-fibrineuse; à 21 ans, appendicite, puis salpingite; à 22 ans, syphillis traitée; depuis, 3 grossesses normales; 2 fausses couches accidentelles; en août 1954 une fausse couche provoquée; depuis, furonculose — amaigrissement.

Le 17/9/54: Hospitalisée dans un Service de Médecine. T.A. normale, urée 0,25.

Le 18/9/54: EEG.

Le 29/9/54: Hospitalisée dans le Service de Neuro-chirurgie: nouvelles crises comitiales atypiques; la dernière suivie d'une hémiplégie gauche progressive — obnubilation.

Numération globulaire: Globules rouges 4.240.000; Globules blancs 24.600; 77 pour cent polynucléaires neutrophiles; 29 pour cent lymphocytes.

Le 30/9/54, après une ventriculographie qui confirme le diagnostic de masse frontale droite, on procède sous anesthésie locale à l'ablation en masse d'un gros abcès multiloculaire semblant d'origine corticale correspondant à l'aire 8 et à la partie postérieure de l'aire 9.

Evolution: Très bonnes suites opératoires.

COMMENTAIRES EEG (fig. 3).

L'examen EEG pratiqué 36 heures environ après une crise de Grand Mal montre survenant sur une activité de base quasi-normale

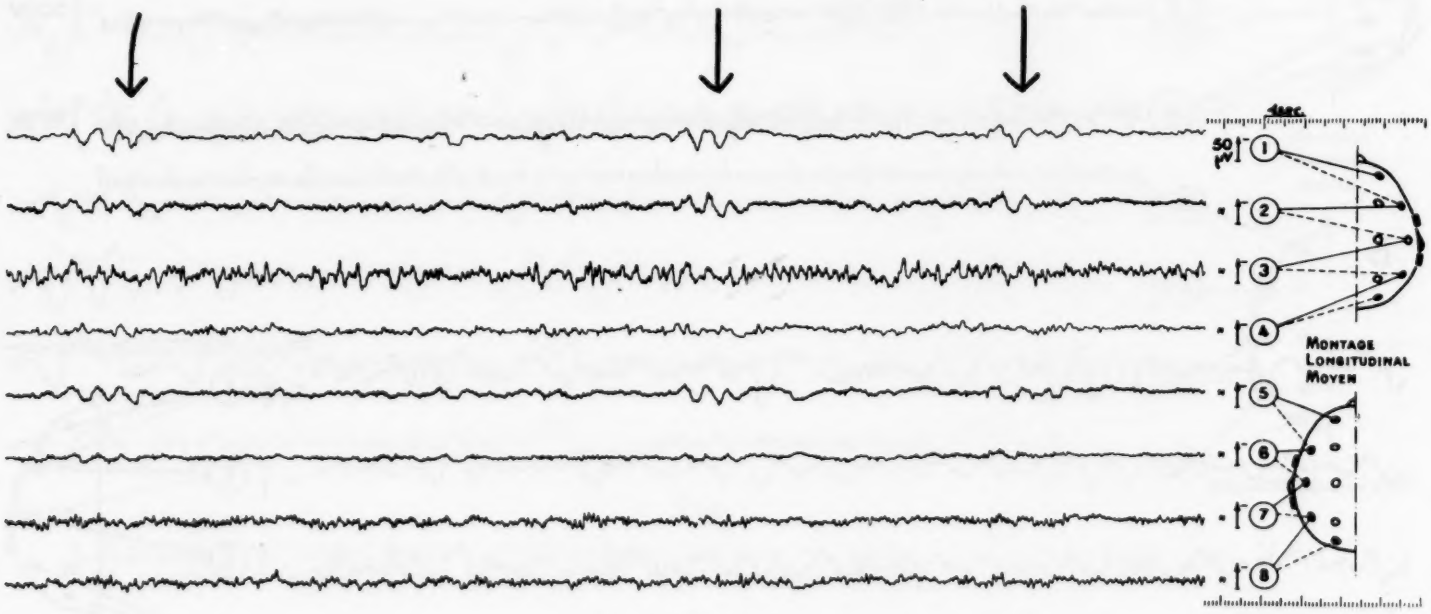

Fig. 3

Montage longitudinal moyen. *Abcès multiloculaire pré-rolandique droit.* Voir dans le texte le commentaire de l'EEG de l'observation nº 1.

à gauche, perturbée par des anomalies lentes peu amples de la bande théta sur la région pariéto-temporale droite, des décharges lentes constituées par le groupement de trois ou quatre ondes lentes monophasiques négatives nettement plus amples que le reste des potentiels recueillis. Ces anomalies surviennent de façon *périodique* (une décharge toutes les 10 ou 15 sec.). Elles sont focalisées au niveau de la région frontale pré-rolandique droite. Leurs caractères propres (stéréotypie de la morpho-

logie en particulier) sont rendus plus évidents par leur survenue sur une activité de base locale de faible amplitude. On signale la discrétion de la diffusion de ces anomalies sur la région préfrontale controlatérale.

Observation n° 2: L. . . . Yvonne, 54 ans.

Le 7/2/57: apparition de violentes céphalées fronto-pariétales médianes — sensations vertigineuses — algidité — température 37° C. — T.A. 17-10½.

Les jours suivants: persistance des mêmes signes subjectifs — apparition d'une légère fièvre (38°) — Babinski gauche — F.O.: légère dilatation veineuse, pupilles à bord mal limité surtout à gauche.

riens; hémianopsie latérale homonyme gauche; stase bilatérale.

Le 18/2/57: 1er EEG.

Le 18/2/57 après une ponction ventriculaire qui confirme le diagnostic d'hématome, on évacue par volet occipito-temporal droit un volumineux hématome intracérébral; l'hémorragie s'est d'ailleurs propagée à l'espace sous-dural et à la face interne du lobe occipital.

Evolution: Amélioration immédiate. Bonnes suites opératoires.

COMMENTAIRES EEG (fig. 4).

L'EEG est pratiqué 11 jours après le début de la maladie. Il montre, contrastant avec une quasi normalité de l'activité de base

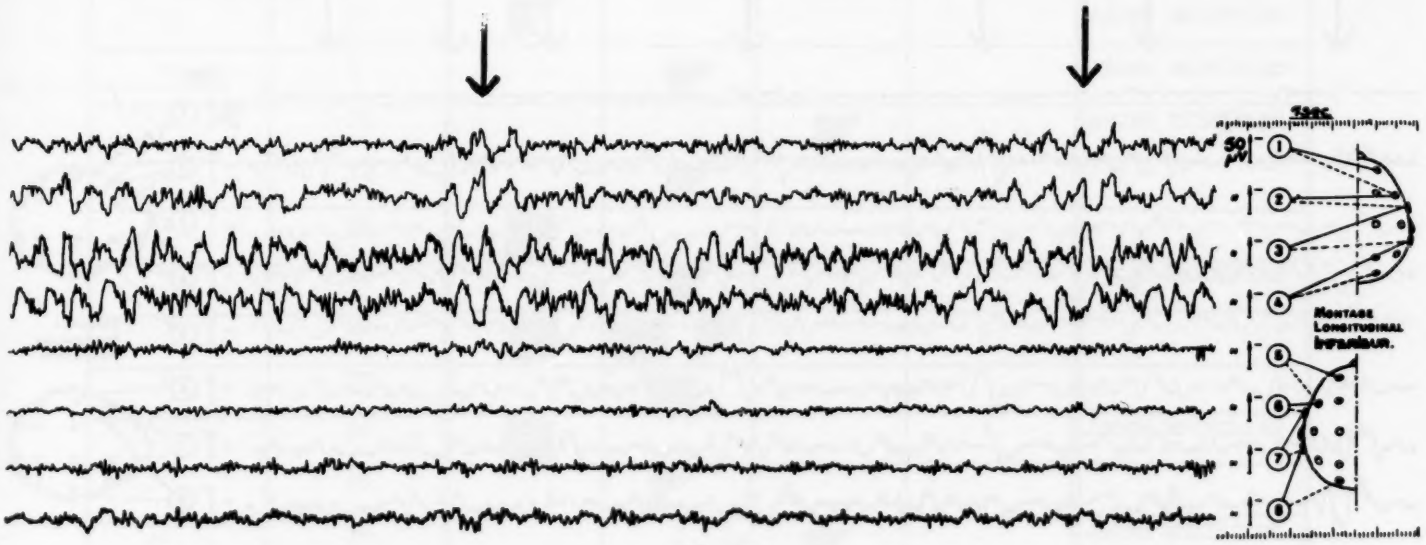

Fig. 4

Montage longitudinal inférieur. *Hématome sous-dural temporal droit.* Voir dans le texte le commentaire de l'EEG de l'observation n° 2.

Numération globulaire: Globules rouges: 3.650.000; Globules blancs: 7.700; 73 pour cent polynucléaires neutrophiles; 23 pour cent lymphocytes; Urée: 0,45.

Antécédents: hypertension modérée, connue depuis un an environ — épisode grippal avec signes pulmonaires (expectoration) fin janvier 1957.

Le 16/2/57: Hospitalisation: malade somnolente, T.A. 13-8; douleurs à la pression de la fosse temporale un peu plus marquée à droite. Pas de signes déficitaires moteurs; persistance des céphalées; hyperesthésie cutanée à la piqûre; pas de troubles de la sensibilité profonde; réflexes normaux; pas de troubles cérébello-vestibulaires ou sphincté-

à gauche, d'importantes anomalies hémisphériques droites. Ces anomalies consistent d'une part en un rythme delta assez ample comportant de nombreux éléments à front raide, temporo-occipital (cette activité lente polymorphe est surchargée par un rythme de base un peu plus ample et plus lent que celui du côté sain) et d'autre part en bouffées delta polymorphes un peu plus amples dont le champ électrique intéresse toutes les dérivations hémisphériques droites. Ces bouffées se répètent avec une stéréotypie approximative, une, deux ou trois fois toutes les vingt secondes. Cette survenue à *tendance périodique* devient plus sensible lorsqu'on examine le tracé dans son ensemble.

Observation nº 3: C. . . . Lucette, 17 ans.

Depuis trois mois, syndrome progressif d'hypertension intra-crânienne: céphalées, vomissements.

Depuis 8 jours: baisse de l'acuité visuelle, hoquet, somnolence.

Le 29/3/57: hospitalisée dans le Service. Examen neurologique: obnubilation; légère hypotonie droite; réflexes ostéotendineux faibles, abolis aux membres inférieurs; cutanés plantaires indifférents; paralysie faciale droite; stase au F.O.

Numération globulaire: Globules rouges: 4.960.000; Globules blancs: 7.400; 80 pour cent de polynucléaires neutrophiles; 16 pour cent de lymphocytes.

Le 29/3/57: *Artériographie gauche* montrant l'injection d'une tumeur pré-rolandique basse gauche; douleur à la pression de la fosse temporale droite; paralysie du VI gauche.

Le 30/3/57: 1er EEG.

Le 31/3/57, sous anesthésie locale, l'intervention chirurgicale, après ablation d'un couvercle de cortex correspondant aux aires 6 et 8 permet d'enlever complètement une tumeur sous-corticale très hémorragique bien limitée. Il s'agit histologiquement d'un glioblastome isomorphe.

Evolution: Bonnes suites opératoires.

COMMENTAIRES EEG (fig. 5).

Le premier EEG est pratiqué environ trois mois après les premiers troubles cliniques, 8 jours après une « poussée » évolutive. Le tracé montre d'emblée des altérations complexes et des modifications du rythme de base. Il s'agit avant tout de rythmes polymorphes de la bande delta prédominant sur la région prérolandique haute gauche. On reste cependant frappé malgré la diffusion et le polymorphisme des altérations par la survenue, toutes les 3 ou 5 sec., de décharges lentes, peu stéréotypées mais plus amples qui présentent des oppositions de phase inconstantes mais fréquentes sur les régions rolandique et prérolandique haute gauches (alterations *à tendance périodique*).

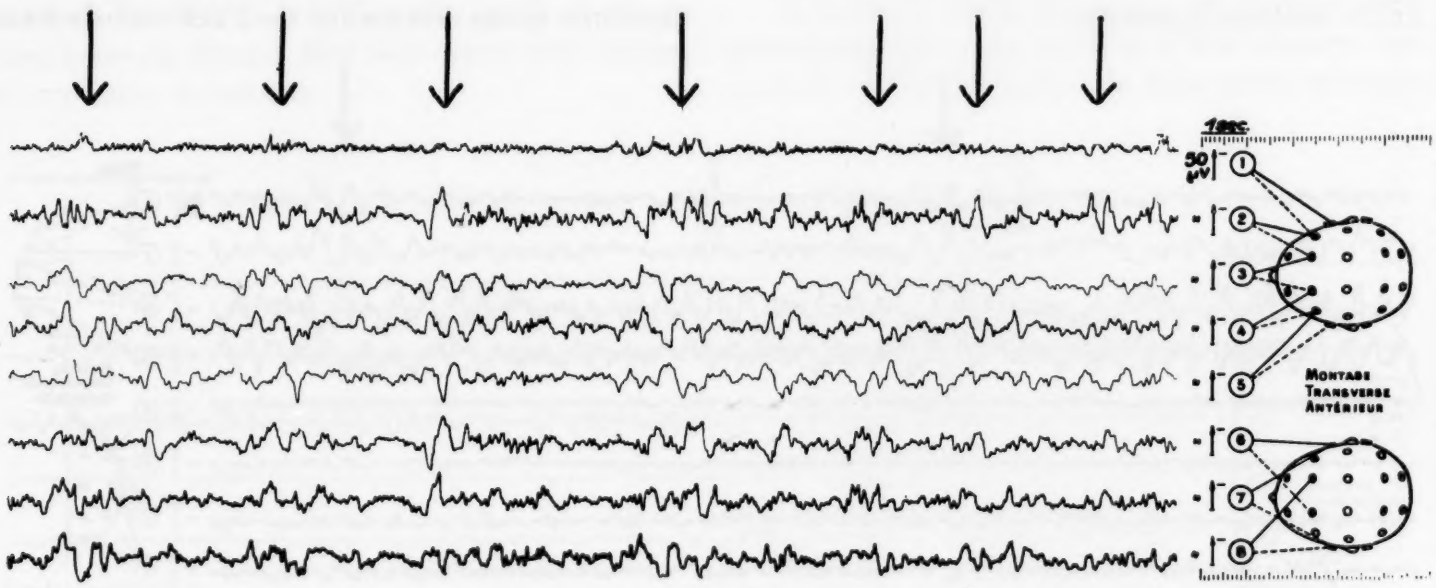

Fig. 5

Montage transverse antérieur. *Gliome rolandique gauche.* Voir dans le texte le commentaire de l'EEG de l'observation nº 3.

RÉSULTATS

Les EEG pré-opératoires de ces trois observations de néoformations rapidement expansives ont en commun des anomalies localisées périodiques ou à tendance périodique. Pour juger la valeur diagnostique électroclinique de telles anomalies, nous avons isolé dans nos observations trois séries de néoformations d'évolution rapide ou évoluant par poussées, à savoir:

I — 19 cas d'abcès ou d'empyèmes.

II — 42 cas de collections sanguines.

III — 29 cas de tumeurs (16 métastases et 13 gliomes examinés lors d'une poussée évolutive).

I — *Abcès et empyèmes*

Cette série comporte 15 abcès et 4 empyèmes.

A) *La série des abcès* (tableau I A) se caractérise par la précocité de la date des examens électriques (5 EEG moins de 7 jours l'abcès était unique 8 fois multiloculaire. Dans les abcès uniques la coque était en voie de formation ou le plus souvent déjà organisée (Le Beau 1949).

Le germe le plus commun était le staphylocoque. On a identifié une fois un streptocoque banal, une fois un exceptionnel nocardia (Testard, Le Beau et coll. 1954). Deux fois enfin les cultures sont restées négatives.

Electriquement et suivant la définition donnée plus haut quatre tracés ont montré

TABLEAU - IA - ABCES

No. Du Cas	Age	Date de l'EEG par rapport au debut de la maladie				REMARQUES
		< 1 sem.	< 2 sem.	< 1 mois	< 2 mois	
1	4	◤				ABCES MULTIPLES
2	6		◤			ABCES MULTIPLES
3	20			◤		ABCES MULTIPLES
4	22		◤			
5	23	■				
6	29		◤			ABCES MULTIPLES
7	29	■	■ ◤			
8	32		■			
9	32	■				ABCES MULTIPLES
10	33		◤			
11	38			◤		ABCES MULTIPLES
12	45				◤	
13	45			◤		ABCES MULTIPLES
14	47	◤				
15	67		◤			ABCES MULTIPLES

ABCES. Les carrés noirs indiquent les tracés présentant des anomalies latéralisées *périodiques.* Les triangles indiquent des tracés présentant des anomalies latéralisées *à tendance périodique.*

après le début des troubles cliniques, un seul EEG plus de deux semaines et moins d'un mois après les premiers symptômes de l'affection).

La distribution des malades en fonction de l'âge montre la dispersion habituelle (Loeser 1957).

Les constatations anatomiques, lors de l'intervention, sont elles aussi banales: présence dans tous les cas d'œdème cérébral. Sept fois des anomalies *périodiques*; tous les autres, des anomalies *à tendance périodique.*

Parmi les 4 malades présentant des altérations périodiques sur leurs tracés, trois ont été examinés avant le septième jour de l'affection clinique, le quatrième avant le quinzième jour. L'un de ces tracés révélait des phénomènes paroxystiques localisés survenant toutes les deux secondes réalisant ainsi des décharges subintrantes de périodicité brève.

TABLEAU - 1B - EMPYEMES

No. Du Cas	Age	Date de l'EEG par rapport au debut de la maladie				REMARQUES
		< 1 sem.	< 2 sem.	<1 mois	< 2 mois	
1	21	●				
2	29	◤				COLLECTION TENDUE
3	43		◤	◤	●	COLLECTION TENDUE
4	46	◤				COLLECTION TENDUE

EMPYÈMES. Les ronds noirs indiquent les tracés sans anomalies latéralisées périodiques ni anomalies latéralisées à tendance périodique. Les triangles, comme dans le tableau I A, indiquent les tracés présentant des anomalies latéralisées à tendance périodique.

B — *Les empyèmes* (4 cas) tableau I B. Trois tracés montrent des altérations à *tendance périodique* (deux pratiqués dans la première semaine de l'évolution, un avant la fin du premier mois). Dans les quatre cas [1] il s'agit macroscopiquement d'empyèmes sous-duraux typiques: collection purulente plus ou moins tendue, semblant parfois jaillir d'une scissure ou d'un sillon; cortex rouge plus ou moins œdématié; une fois, un doute reste possible quant à l'existence d'un abcès intra-parenchymateux associé: il s'agit du cas où plusieurs EEG pré-opératoires ayant été pratiqués; on assiste sur le 3ème examen électri-

TABLEAU - II - HEMATOMES SPONTANES

No. Du Cas	Age	Date de l'EEG par rapport au debut de la maladie				REMARQUES
		< 1 sem.	< 2 sem.	< 1 mois	< 2 mois	
1	27		●			
2	28		●			
3	38	●				
4	43			●		
5	47	●				
6	48			●		
7	48			●		
8	54		●			
9	54		●			
10	55		◤			KPISODE GRIPPAL
11	57			●		
12	60		●			
13	61		●			
14	63		●			
15	69	●				
16	72	●				

HÉMATOMES SPONTANÉS. Voir la légende du tableau I B.

[1] Un 5ème cas récent d'empyème sous-dural examiné au 15ème jour de la maladie montre des anomalies latéralisées, assez diffuses, à tendance périodique et une dépression relative de l'activité de base locale.

que pré-opératoire à la disparition des anomalies à tendance périodique; cette disparition paraît correspondre à l'extension secondaire de l'abcès sous-dural (cas n° 3, tableau I B).

lection purulente sous-durale qui avait d'ailleurs, en raison d'une dépression de l'activité cérébrale sous-jacente, fait évoquer un hématome juxta-dural.

TABLEAU III - HEMATOMES TRAUMATIQUES

No. Du Case	Age	Date de l'EEG par rapport au debut de la maladie				REMARQUES
		< 1 sem.	< 2 sem.	< 1 mois	< 2 mois	
1	21	●				
2	30	●				
3	32	●				
4	33	●				
5	34				●	
6	34			●		
7	34			●		
8	36		●			
9	37	●				
10	43			●		
11	43			●		
12	43	●				
13	43	●				
14	45	●				
15	46			◤		DANS LOBE ATROPHIQUE
16	47	●				
17	48				●	
18	51	●				
19	53		●			
20	53	●				
21	54			●		
22	54			●		
23	56		●			
24	56		●			
25	60				●	
26	60		●			

HÉMATOMES TRAUMATIQUES. Voir la légende du tableau I B.

Le cas (n° 1, tableau I B) ne comportant pas de figures à tendance périodique se caractérise par la précocité de l'examen EEG (4ème jour) et la relative étendue de la col-

II — *Hématomes*

Nous avons différencié les hématomes spontanés (16 cas) et les hématomes traumatiques (26 cas).

A — *Hématomes spontanés* (tableau II) Ce groupe est cliniquement et électriquement très homogène, les malades étant examinés dans le Service environ 15 jours après le début de leur maladie ; 14 de ces malades présentaient un hématome intra-cérébral avec les signes électriques habituellement rencontrés dans ce genre d'accident vasculaire ; une fois il s'agissait d'hématome sous-dural et de collapsus cérébral chez un sujet âgé avec un EEG très perturbé qui avait d'ailleurs fait porter à tort le diagnostic d'hémorragie intra-cérébrale ; une fois enfin, d'un hématome intra-cérébral et sous-dural qui se présentait (observation rapportée n° 2) électriquement avec des phénomènes à *tendance périodique*. On souligne que ce dernier cas, électriquement observé au 11ème jour de la maladie, est en fait assez complexe puisque l'accident hémorragique est survenu au 15ème jour d'un épisode grippal qui devait persister encore pendant deux semaines, et que la collection sanguine était importante.

B — *Hématomes traumatiques* (tableau III). Ce groupe est moins homogène puisqu'on y retrouve des accidents vasculaires de type divers : 15 hématomes sous-duraux, 9 hématomes intra-cérébraux (deux fois associés à des hématomes sous-duraux, une fois à un hématome extra-dural, une fois à une hémorragie sous-arachnoïdienne, une fois à un ramollissement plus ancien), un extra-dural, une fois enfin il s'agissait d'un hydro-hématome sous-dural.

Dans ce groupe d'hématomes traumatiques, un EEG seulement, pratiqué moins d'un mois après le début de la maladie en cause, présente des accidents *à tendance périodique* ; là encore il s'agit d'une lésion complexe : l'opération découvrant dans un lobe temporal atro-

TABLEAU - IV - METASTASES

No. Du Cas	Age	Date de l'EEG par rapport au debut de la maladie							REMARQUES
		< 1 sem.	< 2 sem.	< 1 mois	< 2 mois	< 6 mois	< 1 an	> 1 an	
1	41					●			KYSTIQUE
2	42			◤					KYSTIQUE
3	45		●						MULTIPLES
4	46		●						
5	49			●					
6	49				●				
7	53			◤					ABCEDEE
8	55					●			
9	56					◤			PSEUDO KYSTE
10	56		◤			●			
11	57			●					
12	57				●				
13	57		●						
14	63			●					
15	64					●			KYSTIQUE
16	65					●			KYSTIQUE

MÉTASTASES. Voir la légende du tableau I B.

phique, siège d'un ramollissement ancien, un hématome intra-cérébral particulièrement bien collecté.

En bref, dans cette série d'accidents hémorragiques deux EEG seulement présentent des phénomènes à *tendance périodique.*

III — *Les tumeurs*

Ce dernier groupe, par définition hétérogène, comporte des métastases cérébrales d'évolution rapide (16 cas) et certains gliocas), la relative rareté des métastases multiples (un cas certain).

Electriquement, quatre tracés montrent des anomalies localisées à *tendance périodique.* Une fois, il s'agit d'une métastase abcédée, deux fois d'une métastase kystique. Le quatrième cas (métastase unique, bien limitée, non kystique) comporte deux EEG pré-opératoires: le premier avant le quinzième jour avec des anomalies à tendance périodique, le second au quatrième mois après le début des

TABLEAU V - GLIOMES A POUSSEES EVOLUTIVES

No. Du Case	Age	Date de l'EEG par rapport au debut de la maladie							REMARQUES
		<1 sem.	< 2 sem	< 1 mois	<2 mois	< 6 mois	<1 an	>1 an	
1	15	↑	◤						TUMEUR LIMITEE, DURE, ETENDUE
2	17				↑◤				TUMEUR LIMITEE, MOLLE, RESISTANTE
3	17	↑		↑	●				
4	34							↑◤	TUMEUR DURE COMME DU BOIS
5	45					↑●			
6	49		●		↑◤				TRES PROFONDE
7	50	↑●	●						TUMEUR ENVAHISSANTE
8	54	↑	●						
9	55	↑	●						TUMEUR POLYKYSTIQUE
10	56			↑	●				
11	59					↑●			
12	61	↑	◤	●					TUMEUR PROFONDE DURE ENVAHISSANTE
13	66				↑●				

TUMEURS À POUSSÉES ÉVOLUTIVES. Voir la légende du tableau I B. Les flèches indiquent une poussée évolutive. La colonne dans laquelle la flèche se trouve, indique la date de la poussée évolutive par rapport au premier symptôme clinique.

mes examinés électriquement lors d'une poussée évolutive (13 cas).

A — *Les métastases* (tableau IV). Cette série se caractérise par la relative précocité des examens EEG, tous pratiqués avant le 6ème mois de l'évolution et par la distribution des malades en fonction de l'âge (entre 40 et 50 ans).

Les constatations anatomiques montrent la relative fréquences des tumeurs kystiques (5 troubles où ce type d'anomalies a disparu (cas n° 10, tableau IV).

Dans tous les cas, quelle que soit la localisation, le compte-rendu opératoire signale un certain degré d'œdème.

B — *Les gliomes à poussées évolutives* (tableau V). Cette série de 13 cas est très hétérogène aussi bien en ce qui concerne la distribution des malades en fonction de leur âge, que des caractères histologiques et anatomi-

ques des gliomes (parfois astroblastiques, parfois kystiques, plus ou moins « durs », plus ou moins infiltrants) ou que le moment de la poussée évolutive, par rapport au début de la maladie.

Electriquement, on a retrouvé 5 fois des phénomènes *à tendance périodique* et chaque fois lorsque l'EEG avait été pratiqué peu de

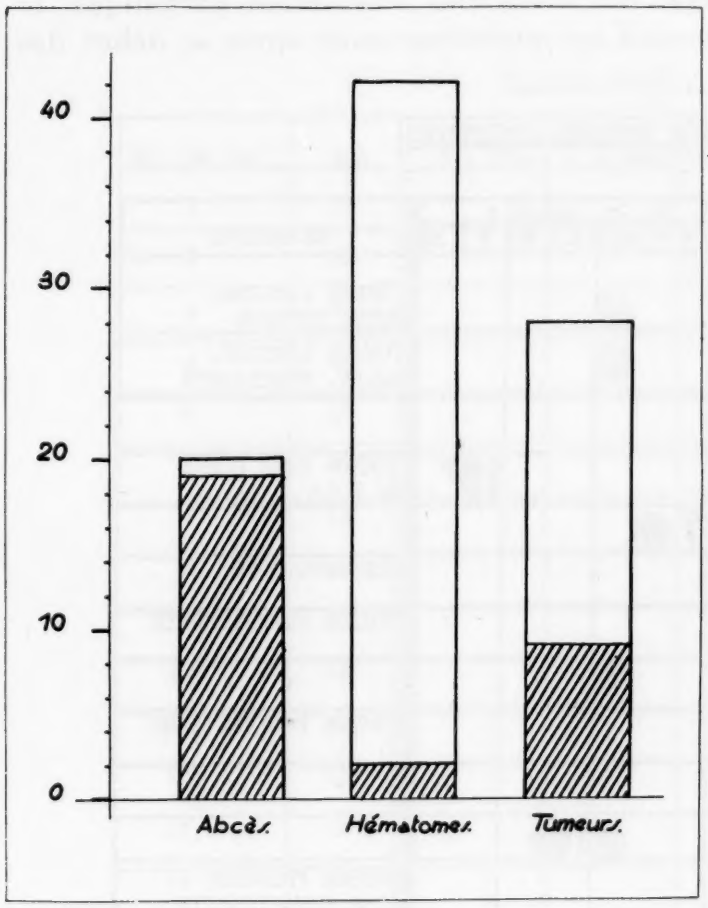

TABLEAU VI

DIAGRAMME représentant en grisé le nombre des tracés qui comportent des altérations latéralisées périodiques ou à tendance périodique par rapport au nombre de cas de *néoformations purulentes* (20 au total, soit 15 abcès, 4 empyèmes et 1 métastase abcédée; le cas non grisé — nº 1 des empyèmes, tableau I B — représente un empyème enregistré très précocement.) d'*hématomes* (42 au total) et de *tumeurs* (28 au total, soit 15 métastases non abcédées et 13 gliomes à poussées évolutives).

jours après le début de la poussée. Deux fois deux examens pré-opératoires ont été pratiqués à des distances variables de la poussée. Dans ces deux cas, seul l'EEG le plus proche de la poussée évolutive présentait des altérations à tendance périodique (cas nº 6 et nº 12, tableau V).

Ces trois séries montrent donc (tableau VI) des altérations localisées périodiques ou à tendance périodique:

1 — chez les 20 porteurs de néoformations abcédées (15 abcès + 3 des quatre empyèmes + une métastase abcédée): dans 19 des cas dont les 15 abcès;

2 — chez les porteurs de néoformations sanguines, dans environ 5 pour cent des cas (2 cas sur 42);

3 — chez les porteurs de néoformations tumorales à évolution rapide ou poussée évolutive (13 cas de gliomes et 15 cas de métastases non abcédées) dans environ ⅓ des cas (9 cas sur 28).

DISCUSSION

Les différences de pourcentage des tracés présentant des altérations périodiques ou à tendance périodique sont significatives dans ces trois séries de cas. La seule présence de telles anomalies permet donc de rendre le plus probable le diagnostic d'abcès, le moins probable celui de collection sanguine.

Cette remarque statistique invite cependant à discuter ces résultats pour préciser la valeur diagnostique des EEG comportant de telles anomalies.

1° *Valeur localisatrice* des anomalies latéralisées périodiques ou à tendance périodique: sur les 31 tracés présentant de telles anomalies, sur les 90 cas étudiés, 30 fois la localisation EEG s'est fondée, au moins en partie, sur la distribution de ces altérations: une fois (gliome dur, infiltrant et très étendu chez un adolescent, tableau V, cas nº 1) cependant, ces altérations ne s'exprimaient que du côté opposé à celui qui présentait les signes électriques lésionnels les plus marqués, sans doute en raison de l'importance des destructions corticales et sous-corticales.

2° *Valeur étiologique* des anomalies périodiques ou à tendance périodique: une première remarque s'impose: ces anomalies surviennent rarement de façon isolée pour représenter à elles seules les signes EEG lésionnels (4 fois sur 31, chaque fois lors d'abcès du cerveau, vus très précocement chez des sujets jeunes: cas 5, 7, 8 et 9, tableau I A). Le plus souvent elles sont associées à des signes évo-

cateurs du type de néoformation en cause. On peut ainsi rappeler rapidement et schématiquement que :

dans les abcès, existe volontiers une activité de base quasi-normale entre les décharges (« intervalles de rythmes sains ») du moins dans les abcès uniques déjà bien limités et que les décharges comportent des éléments particulièrement lents amples et irréguliers (Courjon 1949 ; Ziegler 1952) ;

dans les collections sanguines, le côté lésé présente des altérations dont la plus caractéristique est une asymétrie du rythme de base moins ample et plus lent (Gaches, Dondey et Foncin 1958) ;

dans les tumeurs, les signes lésionnels sont par définition complexes : se manifestant volontiers par une activité delta relativement peu ample et monomorphe dans les métastases et entraînant souvent des « signes à distance » en particulier sur les régions frontales dans les gliomes déjà étendus.

Ainsi les arguments étiologiques, jamais formels, que l'EEG peut apporter, se fondent, non seulement sur la survenue plus ou moins périodique de certaines anomalies, mais également sur la présence d'altérations lésionnelles.

Cette remarque étant faite, la valeur étiologique des anomalies périodiques ou à tendance périodique va dépendre également de leur présence dans d'autres syndromes cliniquement évocateurs de néoformations rapidement expansives. Nous avons pris au hasard certaines observations cliniques de ce type, à savoir 13 cas d'affections diverses ayant pu faire évoquer le diagnostic d'abcès à cause du syndrome infectieux (3 thrombophlébites, 2 méningites cérébrospinales, 4 méningites tuberculeuses, 4 méningo-encéphalites mal étiquetées). Les EEG de porteurs de thrombophlébites ne montraient pas d'altérations à tendance périodique. Parmi les autres, 5 examens mettaient en évidence des anomalies à tendance périodique à *expression bilatérale* synchrone, deux fois asymétrique. Cette asymétrie explicable de façons diverses (prédominance locale du processus pathologique, dépression associée de l'activité corticale) permet de souligner l'importance attachée, dans ce travail, au caractère unilatéral des décharges périodiques.

3° *Valeur physiopathologique* de ces anomalies latéralisées périodiques ou à tendance périodique : en ajoutant aux 104 observations mentionnées, 16 cas de gliomes à évolution progressive nous disposons de 120 dossiers anatomo et électro-cliniques (certains malades ayant subi plusieurs EEG pré-opératoires, nous avons revu 130 tracés) pour tenter d'établir des corrélations entre ces anomalies et des facteurs divers isolés à priori tels que l'âge du malade, son état de conscience pendant l'examen, l'allure évolutive de la maladie, les constatations anatomiques, bactériologiques, autopsiques ou histologiques.

En fait, *certains de ces facteurs ont été décevants tels* :

l'*âge,* qui ne semble jouer aucun rôle, en particulier dans les cas d'abcès ou d'accident hémorragique ; on peut cependant souligner que les altérations à tendance périodique surviennent plutôt en ce qui concerne les métastases et les gliomes, chez les sujets les moins âgés ;

la « condition » du malade lors de l'enregistrement ; nous n'avions malheureusement pas assez de documents pour évaluer de façon précise le degré de conscience du patient ; il convient toutefois de remarquer à ce propos que les anomalies EEG tendent parfois à devenir moins périodiques lors de l'hyperpnée ; nous n'avons pas eu l'occasion de pratiquer d'enregistrement pendant le sommeil (Salou 1954) ;

la nature infectieuse de la maladie et l'identification du *germe* en cause lorsqu'il n'y a pas d'abcès constitué. Nous n'avons pas, en effet, retrouvé de phénomènes à tendance périodique dans les 3 cas de thrombophlébite, ni dans 6 des cas de méningites confirmées ;

l'œdème découvert à l'intervention ; il s'agit là en effet d'une éventualité presque toujours réalisée et ni ses degrés ni ses modalités (œdème sanglant) ne permettent d'établir la moindre corrélation avec les phénomènes électriques ; les *localisations,* très diverses, des néoformations non plus.

Par contre, *d'autres facteurs paraissent intéressant à souligner* :

l'évolution de l'affection; ce facteur est particulièrement net si l'on regroupe tous les cas de gliomes (29) où 6 fois existaient des anomalies à tendance périodiques, 5 fois en rapport avec une évolution initialement ou secondairement rapide (dans le sixième cas il s'agissait d'une tumeur sous-corticale, à évolution lente mais « dure comme du bois »: cas n° 4, tableau V);

certains caractères anatomo-pathologiques, par ailleurs, réalisent un facteur sans doute significatif et permettent d'opposer les néoformations molles, diffuses aux néoformations mieux limitées, peu compressibles ou même franchement dures. Cette opposition qui se fonde sur des caractères aussi divers que la nature histologique, la tendance à l'enkystement, le volume de la néoformation en fonction de sa localisation, etc.... permet en effet de grouper les abcès collectés, les gliomes et les métastases limitées et compactes et même certaines collections sanguines. Un tel ensemble présente un grand pourcentage de tracés comportant des éléments périodiques ou à tendance périodique qui sont rencontrés:

quinze fois dans 15 abcès du cerveau;

trois fois (cas n° 2, 3 et 4, tableau I B) dans 4 empyèmes sous-duraux. Le quatrième cas est caractérisé par la relative diffusion et sans doute la faible tension de la collection purulente sous-durale;

deux fois (cas n° 10, tableau II; cas n° 15, tableau III) dans 2 cas de collections sanguines particulièrement tendues et bien limitées;

trois fois (cas n° 2, 7 et 9, tableau IV) dans 3 cas de métastases particulièrement compactes. Une fois (cas n° 10, tableau IV) cependant sur 13 autres métastases, existaient des anomalies localisées à tendance périodique;

cinq fois (cas n° 1, 2, 4, 6 et 12, tableau V) sur 5 cas de gliomes particulièrement durs ou tendus. Une fois cependant existaient, comme on l'a signalé, des anomalies localisées à tendance périodique parmi les 24 autres gliomes.

Par contre le développement de kystes intra-tumoraux ne paraît pas influer sur l'expression électrique; nous n'avons pu étudier en détail d'ailleurs, le volume très variable de ces kystes souvent multiples.

Certains aspects histologiques péri-lésionnels: malgré le très petit nombre de pièces permettant d'étudier les modifications périlésionnelles, il n'est pas sans intérêt de signaler qu'on a parfois (cas d'abcès) mis en évidence un « œdème-nécrose » étendu loin de la néoformation, mais limité à la substance blanche en respectant le cortex et partiellement les fibres en U. En effet une telle constatation rappelle les descriptions histologiques des lésions de certaines encéphalites subaiguës (Radermecker 1958) dont on sait l'expression électrique typiquement périodique.

Ces différents facteurs, concernant le mode d'évolution et certains caractères anatomiques pourraient être en rapport avec un *mode de réaction périlésionnelle* éventuellement voisin dans ces néoformations et dans les leucoencéphalites subaiguës. La tendance périodique des altérations électriques serait ainsi rattachée à ce processus parenchymateux périlésionnel. Il s'agit là d'une suggestion d'autant plus timide que les critères de définition choisis dans ce travail sont sans doute à la fois beaucoup trop larges en ce qui concerne les aspects électriques et trop étroits en ce qui concerne le choix des cas cliniques. Si une telle hypothèse pouvait être vérifiée, il resterait encore à expliquer le mode très surprenant de survenue temporelle des altérations EEG à tendance périodique qui reproduisent ou évoquent souvent de véritables décharges épileptiques d'origine sous-corticale (Bates 1958).

CONCLUSION

Les résultats de l'étude électro-clinique de différentes néoformations d'évolution rapide et les comparaisons établies entre ces néoformations d'évolution rapide d'une part, et des néoformations d'évolution progressive ou des affections non néoformatives, d'autres part, confirment donc la valeur diagnostique EEG des anomalies latéralisées périodiques ou à tendance périodique. Celles-ci se rencontrent essentiellement dans les néoformations rapidement expansives et sous forte tension. Leur valeur diagnostique paraît considérable dans

les abcès du cerveau. Au contraire, elles ne sont observées que rarement dans l'évolution des gliomes ou des métastases, qu'exceptionnellement dans les hématomes intra-craniens.

RÉSUMÉ

Cette étude a été suggéré par la présence, sur les EEG de certains abcès du cerveau, d'anomalies stéréotypées, latéralisées et périodiques. Elle porte sur les corrélations électrocliniques de décharges lentes latéralisées, plus ou moins stéréotypées, périodiques ou à tendance périodique dans différents groupes de cas cliniques :

néoformations d'évolution rapide (15 abcès du cerveau, 4 empyèmes) ;

néoformations d'évolution progressive régulière ou par poussées (16 hématomes spontanés, 26 hématomes traumatiques, 16 métastases, 13 gliomes à poussées évolutives) ;

affections non néoformatives (méningo-encéphalites de types divers).

Les comparaisons établies entre ces différents groupes montrent que les anomalies latéralisées périodiques ou à tendance périodique, rencontrées essentiellement dans les néoformations rapidement expansives, prennent une valeur diagnostique particulière dans les abcès du cerveau (15 fois présentes dans 15 cas d'abcès). Ces anomalies ne s'observent, en effet, que rarement dans l'évolution des gliomes et des métastases et qu'exceptionnellement dans les hématomes intra-craniens (présentes dans moins de 5 pour cent des cas).

SUMMARY

This study was suggested by the observation that the EEG in certain cases of brain abscess showed stereotyped lateralized and periodic electrographic disturbances. The present study deals with the investigation of the correlation between this type of electrographic disturbance and the following clinical syndromes :

Rapidly progressive expanding lesions (15 brain abscesses, 4 empyemas) ;

Expanding lesions with a regular progression or with an interrupted progression in bouts (16 spontaneous hematomas, 26 post-traumatic hematomas, 16 metastases, 13 gliomas characterized by a progression with exacerbations) ;

Non-expanding lesions (different types of meningo-encephalitis).

A comparison which was carried out between these different clinical conditions showed that lateralized abnormalities of a periodic type or with a tendency to periodicity are mostly encountered in rapidly expanding lesions and assume a particular diagnostic value in brain abscesses (this disturbance was found 15 times in 15 brain abscesses). These abnormalities are only rarely present during the progressive development of gliomas or metastase and are only exceptionally encountered in intracranial hematomas (incidence in this group was less than 5 per cent of the cases).

ZUSAMMENFASSUNG

Die Untersuchungen, welche in dieser Arbeit mitgeteilt werden, fussen auf der Beobachtung, dass bei gewissen Hirnabszessen das EEG stereotypierte, lateralisierte und periodische Störungen aufweist. Die vorliegende Arbeit untersucht die gegenseitigen Beziehungen zwischen diesen elektrographischen Veränderungen und den folgenden klinischen Syndromen :

Rasch sich entwickelnden Neubildungen (15 Hirnabzesse, 4 Empyeme).

Neubildungen, welche sich regelmässig progressiv oder in Schüben entwickeln (16 Spontanhämatome, 26 traumatische Hämatome, 16 Metastasen, 13 in Schüben sich entwickelnde Gliome).

Affektionen ohne Neubildungen (verschiedene Arten von Meningoenzephalitiden).

Die Vergleichsuntersuchungen, welche an diesen verschiedenen Gruppen von Gehirnaffektionen ausgeführt wurden, zeigen, dass lateralisierte Störungen mit einem periodischen Charakter oder mit einer Tendenz zur Periodizität besonders bei rasch sich entwickelnden Neubildungen angetroffen werden und von besonderem diagnostischen Wert bei Gehirnabzessen sind (diese Veränderungen waren 15 mal vorhanden in 15 Fällen von Gehirnabzessen). Diese Störungen werden in der Tat, während der Entwicklung von Glio-

men oder von Metastasen nur selten beobachtet und nur ausnahmsweise werden sie angetroffen bei intrakraniellen Hämatomen. (Inzidenz weniger als 5 Prozent der Fälle).

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PRINTED IN CANADA

THE ELECTROENCEPHALOGRAPHIC EFFECTS OF METHYLPENTYNOL

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(Received for publication: February 17, 1958)

Methylpentynol (Oblivon), one of the vinyl-ethynyl carbinols, was introduced into therapeutics by Margolin *et al.* 1941. It is 3-methylpentyne-ol-3, with a structural formula $HC = C.C.(CH_3)OH.CH_2CH_3$.

Early reports were unanimous in emphasizing the drug's distinct paucity of toxic complications (Allen and Krongold 1951; Hirsh and Orsinger 1952; Malone *et al.* 1952) and human subjects have received oral doses of between 0.1 - 1.5 g. daily for as long as 6 months without presenting any undesirable side-effects (Chevalley *et al.* 1952). Gialdroni and Grassi (1952) were particularly impressed with its high therapeutic coefficient — approximately 20, as compared with that of less than 2 for the commonly prescribed barbiturates.

Recently a number of dissentient publications have drawn attention to the drug's potential toxicity. May and Ebaugh (1953) noted drowsiness, ataxia and slurred speech in 5 patients who had ingested between 3.89 and 10.16 g. of methylpentynol during periods ranging from 2 to 6 days, a confusional episode also being seen in a woman who had swallowed 10 g. of the substance. Glatt (1955) and Lemere (1952) reported toxic sequelae from abuse of the drug, while Cares *et al.* (1953) recorded a fatality with a dose of 4.5 - 6.0 g.

There is a paucity of published data on the electroencephalographic effects of methylpentynol, although Tukel and Tukel (1952) who examined children sedated with 0.25 - 0.75 g. of the substance, remarked that the records exhibited no features attributable to its action. The same view was expressed by Henry (1953) Levin (1953) and Lanzoni (1955), but Williams (1954) found that 6 of 15 individuals administered a single oral dose of 0.5 g. methylpentynol showed slight or moderate 18-30 per sec. beta activity in the EEG tracings.

However, these workers were primarily motivated to find a drug which, administered prior to encephalography, would produce sedation or sleep without significantly modifying the ensuing waking or sleeping electroencephalogram. To this end, methylpentynol was given solely by mouth, in single doses, and to a maximum of 1.0 g.

In order to supplement such data, we have performed electroencephalography after repeated and larger oral doses of the substance and following intravenous administration. In all instances the records were obtained when the subjects were awake. Electroencephalography was also carried out on a number of subjects who had developed toxic manifestations ascribable to methylpentynol.

METHODS

Following the admission of two patients (cases 1 and 2) with methylpentynol intoxication to this hospital, and who received an EEG both at the height of the disturbance and subsequently when all drugs had been withdrawn for at least a week, the opportunity was taken to investigate an additional 18 subjects (cases 3-20) the majority of whom received 0.5 g. q.d.s. of methylpentynol by mouth for 5 days only. In the last group of patients, a control EEG was performed during a prior 5 day period when they were receiving inert capsules only, and also on the last day of the course of methylpentynol. To confirm that the changes in the records ascribed to methylpentynol were in fact reproduceable, three other individuals (cases 21-

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23) were injected intravenously with the substance at a rate of 0.1 g. per min. to a maximum of 3 g., continuous electroencephalography being performed, the time at which persistent nystagmus on conjugate lateral gaze and fast activity in the tracings appeared being both noted.

The above series of 23 individuals included 9 males and 14 females with an age distribution from 19-60 years and a weight range from 49.1 to 83.6 kg. None of these patients suffered from epilepsy nor were any found to have a significant abnormality of the electroencephalogram apart from that attributable to methylpentynol. Factors known to modify the response to drugs such as previous drug addiction, brain injury, hepatic or renal impairment or anaemia were excluded as far as possible.

The EEGs were obtained with an Ediswan apparatus, the standard bipolar technique being employed with stick-on electrodes and an amplification of 7.5 mm. representing 50 μV.

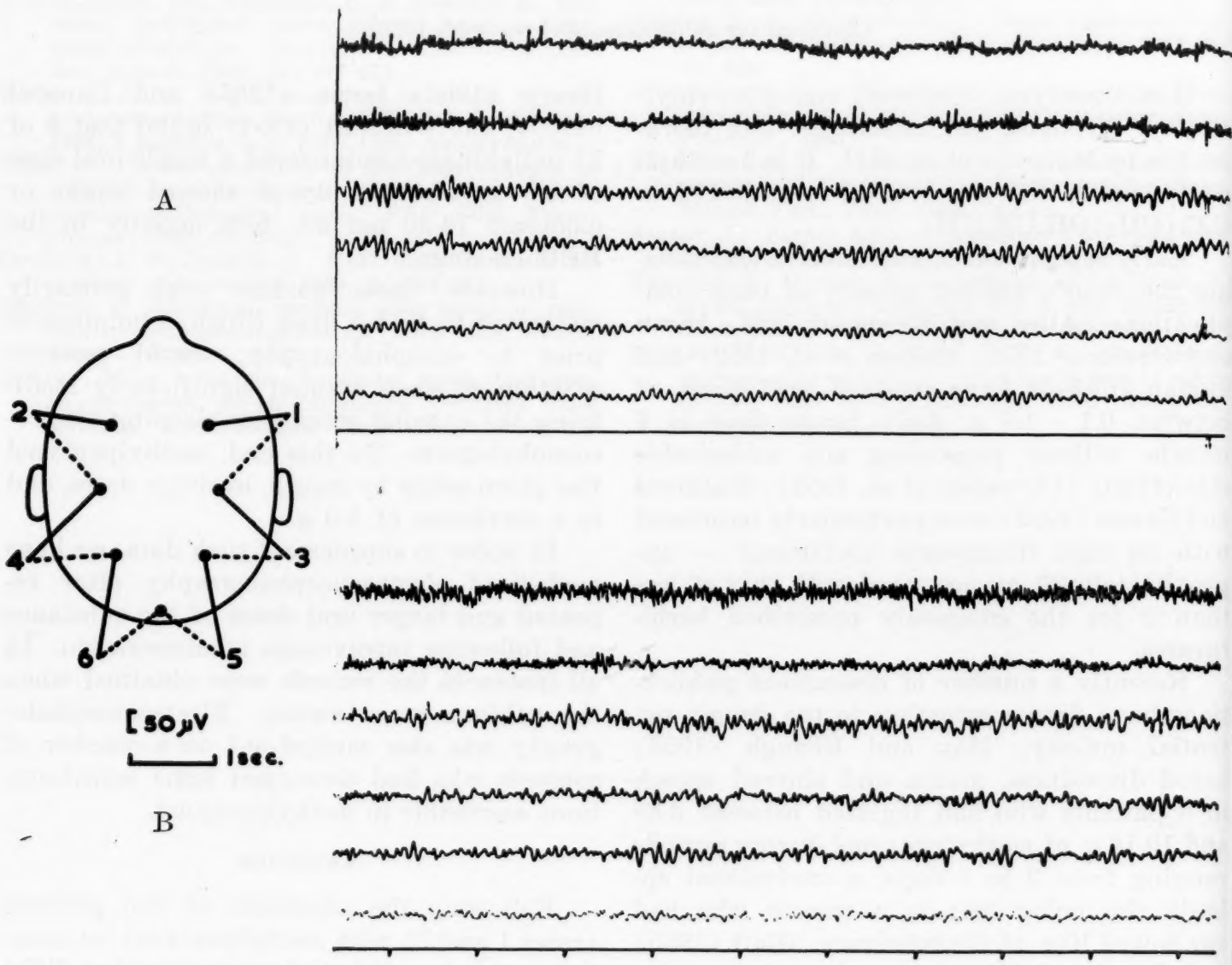

Fig. 1

Case 3. The upper tracing (A) is before administration of methylpentynol. The lower tracing (B) is after administration of methylpentynol 3 g. and shows fast activity in fronto-central areas with some slow activity also present.

EEG Gradings

The resultant electroencephalograms were subdivided into three:

(1) those with no change in the record as compared with the control tracing;

(2) those with minimal change as represented by the presence of low voltage fast

activity confined to the frontal and central areas of the brain; and

(3) those with maximal change, amounting to fast activity seen as far back as the parietal region with slowing of the dominant post-central activity in the most severe instances (fig. 1, A and B).

Clinical Gradings

The responses of individuals receiving methylpentynol by mouth was categorized into three, so that objective clinical measurements might be equated against the respective EEG grading. The unexpected and considerable incidence of toxic phenomena in subjects receiving methylpentynol, determined a classification of nil, minimal and maximal toxic categories, depending on the presence or absence of abnormal signs in the central nervous system.

A maximal toxic reaction (clinical grading 3) presented with pupillary reflex abnormalities, nystagmus, diplopia, ptosis, dysarthria, and tremor of the outstretched tongue. A cerebellar type of ataxia might be found in the limbs, or admixtures of this with posterior column type of ataxy and a positive Romberg's sign. A minimal reaction (clinical grading 2) was epitomized by little more than sustained nystagmus on conjugate lateral gaze and perhaps slight unsteadiness of gait, or drowsiness. No reaction to the drug (clinical grading 1) implied the absence of physical signs although there might be a concomitant mood change such as mild elation.

RESULTS

Table I presents in summary form the clinical diagnosis, dosage of drug administered and the resulting clinical and EEG changes.

TABLE I

EEG changes and clinical disturbances after oral administration of methylpentynol

Case No.	*Sex*	*Age*	*Weight Kg.*	*Diagnosis*	*EEG Change*	*Clinical Disturbance*	*Dosage*
1	M	46	63.6	Paranoid schizophrenia	Max.	Max.	Methylpentynol 10g. and Phenobarbitone 0.26g. during two days
2	F	24	50.5	Anxiety State	Max.	Max.	Methylpentynol 8g. during four days
3	F	28	56.4	Hysteria	Max.	Max.	Methylpentynol 3g. in twenty four hours
4	M	23	71.4	Obsessional illness	Max.	Max.	0.5g. Methylpentynol qds for 5 days
5	F	19	60.0	Hysteria	Max.	Max.	" " " " "
6	M	27	74.5	Hysteria	Min.	Max.	" " " " "
7	F	23	50.5	Asthma	Min.	Max.	" " " " "
8	M	35	62.3	Anxiety state	Min.	Min.	" " " " "
9	F	36	49.1	Anxiety state	Min.	Max.	" " " " "
10	F	20	55.0	Asthma	Min.	Max.	" " " " "
11	F	28	56.5	Asthma	Min.	Max.	" " " " "
12	M	25	75.0	Obsessional illness	Min.	Max.	" " " " "
13	F	60	49.1	Mixed neurotic reaction	Min.	Min.	" " " " "
14	M	30	66.8	Psychopath	Min.	Nil	Methylpentynol 11g. during 8 days
15	M	32	83.6	Mixed neurotic reaction	Nil	Nil	" " " "
16	F	47	76.4	Asthma	Nil	Nil	0.5g. Methylpentynol qds for 5 days
17	F	39	65.0	Phobic anxiety	Nil	Nil	" " " " "
18	F	48	66.7	Asthma	Nil	Nil	" " " " "
19	F	45	59.1	Hysteria	Min.	Max.	" " " " "
20	M	25	60.0	Asthma	Min.	Min.	" " " " "

Correlation between EEG Changes and Clinical Effects of Methylpentynol

The relation between alteration of the EEG and the clinical response to methylpentynol is set out in table II.

From inspection of table II, it is apparent that EEG changes following the administration of methylpentynol are more likely to be

TABLE II

E.E.G. GRADING	CLINICAL GRADING		
	1	2	3
NO CHANGE	4	0	0
MINIMAL CHANGE	1	3	7
MAXIMAL CHANGE	0	0	5

associated with toxic features due to the drug (clinical gradings 2 and 3) than with a normal clinical response to the substance. This was confirmed statistically by using an arc sine transformation, as an analysis with chi square would have been unsuitable. This was achieved by transposing the data to a 2 x 2 contingency table, the total results for the clinical gradings 2 and 3 being combined as were those for the individuals with EEG changes. A significant difference was found between the proportion of patients with EEG alterations but without clinical abnormalities (1 subject out of 5) and the proportion of individuals with both EEG anomalies and clinical toxic phenomena (15 from 15 subjects) the critical ration being 4.29 (p 0.001).

Reproducibility of EEG Changes with Methylpentynol Injected Intravenously

Methylpentynol was given intravenously to three individuals at the rate of 0.1 g. per min. (see table III).

It can be seen that persistent nystagmus on conjugate lateral gaze was noted in 2 of the 3 subjects prior to the emergence of fast activity in the electroencephalogram and at approximately half the total dose level required for the latter.

TABLE III

Case No.	Dose (grams) for appearance of		Total I.V. dose administered grams
	Persistent Nystagmus	Persistent E.E.G. fast activity	
21	0·3	0·8	2·0
22	0·6	NOT SEEN	3·0
23	0·6	1·2	1·5

These EEG changes were such as would have resulted in their being classified as minimal had the drugs been given orally.

DISCUSSION

The presence of 20-30 c/sec. activity in electroencephalographic tracings from the frontal and, less often, the parietal regions, is well recognized as following the administration of barbiturates (Brazier and Finesinger 1945; Lennox 1946) although Cohn and Katznelbogen (1942) suggested that this is not a specific phenomenon, but one that may occur also with cyclopropane anaesthesia and during the early stages of deep sleep.

It is intriguing therefore that similar changes followed the administration of the branched six-carbon alcohol methylpentynol, for apart from Gibbs *et al.* (1953) who noted that the initial effect of ethanol was to decrease the alpha voltage and increase the voltage of rhythms about 20 c/sec., the majority of authors (Davis *et al.* 1941; Engel and Rosenbaum 1945) have in contradistinction observed a slowing of the EEG rhythms as intoxication develops. These apparent discrepancies may be reconciled if interpreted in the light of a recent analysis by Brazier (1954) of the effects of barbiturates on the electroencephalogram. She concluded that the initial fast high voltage activity following the administration of the drug was generated in the cortex itself, being due to a direct action on cortical neurones. Slow rhythms only appeared in the later stages of anaesthesia. Thus the variation in electroencephalographic patterns seen after the ingestion of different substances is not necessarily due to specific

action of a particular drug, but rather to varying levels of drug effect.

Apart from the similarity of the electroencephalograms, Isbell and White (1953) were also struck by the resemblance between the clinical picture of barbiturate and alcohol poisoning, as were Marley and Chambers (1956) for barbiturate and methylpentynol intoxications. These substances are all central nervous system depressants, and while acting ubiquitously on the cerebro-spinal axis, Arduini and Arduini (1953 and 1954) have also shown that the barbiturates and methylpentynol depress the function of the medial part of the reticular formation.

Howells (1956) found nystagmus to be the earliest eye-sign noted after the experimental administration of ethanol, being accompanied by an increase of central nervous system reaction time. Consequently, it is intriguing that sustained nystagmus on conjugate lateral gaze was one of the first abnormalities encountered in individuals responding adversely to methylpentynol, and preceded the appearance of fast activity in the electroencephalogram during the intravenous injection of the drug.

Another point worth comment, is that in spite of a definite correlation between the degree of electroencephalographic alteration and the amount of physical disturbance produced by methylpentynol, it was remarkable how trivial were the changes in the records relative to the gross clinical abnormalities. Had such a picture followed barbiturate administration, the disturbance in the electroencephalogram would have been considerably more pronounced. It is conceivable that the abnormal physical signs may be partly attributable to a neuromuscular blocking action of methylpentynol which is known to occur in animals (Quilliam 1955; Nicholls and Quilliam 1956). Quilliam found that the ratio of the human therapeutic dose (mg/kg.) to the threshold dose of the hypnotic (mg/ml.) required to produce an effect on the isolated frog ilio-fibularis muscle, ranged between 77.5 and 143.0, methylpentynol being one exception with a ratio of 14.3. This suggested that its peripheral action in humans might be negligible. However, the latter ratio was calculated from a mean therapeutic dose of 0.5 g. whereas the majority of our patients received a mean dose of 2.0 g., for which the ratio would be 57.2 and more in keeping with a level at which peripheral blocking effects might be anticipated.

SUMMARY

The presence of 20-30 c/sec. wave activity over the frontal and central regions of the brain was noted in electroencephalograms from individuals who developed toxic phenomena during a 5 day regime of 0.5 g. q.d.s. of methylpentynol by mouth. These abnormalities were seen during the waking state and could be reproduced by the injection intravenously of methylpentynol 0.1 g. per min. to a maximum of 3.0 g.

In the subjects with toxic manifestations, there was a correlation between the degree of electroencephalographic abnormality and the amount of physical disturbance produced by the drug.

RÉSUMÉ

L'apparition d'ondes à une fréquence de 20 à 30 c/sec. au niveau des aires frontales et centrales du cerveau a été notée dans les électroencéphalogrammes de sujets qui développaient des symptômes toxiques après administrations orales journalières de 0.5 g. de methylpentynol pendant 5 jours. Ces anormalités étaient observées quand le sujet était éveillé et pouvaient être reproduites par une injection intraveineuse de 0.1 g. de methylpentynol par minute et montant jusqu'à un maximum de 3 g.

Chez les sujets qui présentaient des symptômes toxiques, il y avait une corrélation entre le degré des anormalités électroencéphalographiques et les symptômes cliniques produits par ce médicament.

ZUSAMMENFASSUNG

Das Auftreten von Hirnwellen mit einer Frequenz von 20-30 Hz. in der Frontal- und Zentralregion des Gehirns wurde im EEG von Individuen beobachtet, welche während einer fünftägigen Behandlung mit peroralen Tagesdosen von 0.5 g Methylpentynol toxische

Phänomene entwickelten. Diese Veränderungen wurden im Wachzustand beobachtet und konnten reproduziert werden duch die intravenöse Injektion von 0.1 g Methylpentynol pro Minute bis zu einem Maximum von 3.0 g. In Individuen, welche toxische Manifestationen zeigten, bestand eine Korrelation zwischen dem Grad der elektroenzephalographischen Aenderungen und der Intensität der klinischen Symptomatologie, welche durch das Medikament produziert wurde.

We should like to thank Dr. Denis Hill and Dr Denis Leigh for their kind permission to publish these findings, and British Schering Ltd. for a generous supply of methylpentynol.

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PRINTED IN CANADA

THE EFFECT OF LARGACTIL ON THE ELECTROENCEPHALOGRAPHIC RESPONSE EVOKED POTENTIAL TO LIGHT STIMULUS IN MAN

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(Received for publication: May 21, 1958)

In earlier works (Cigánek, in press) the human responses to light stimuli (flashes) over the occipital area were described (fig. 1, 2). The first three waves of this response (waves I-III) have characteristics (localization, latency, maximum frequency-resistance, fig. 3) compatible with the assumption that they represent the primary, specific response. The less regular part of the response following wave III is difficult to interpret from our present material. In this work the effect of Largactil on this response has been investigated.

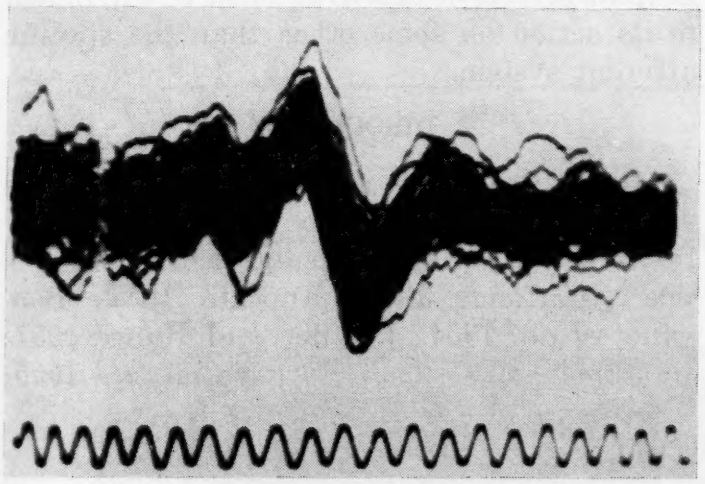

Fig. 1

The human EEG response to light stimulus (flash). Superimposition technique of Dawson, electrodes Oo-Po. The negativity of the electrode Oo results in an upward deflection of the record. The rates of stimulus repetition: 1 per 3 sec. Calib.: 10 msec., 5 μV.

METHODS

As in previous experiments the response to the flash of the stroboscope picked up by scalp electrodes was recorded by the superimposition technique described by Dawson (1947) and photographed from the screen of a cathode ray oscilloscope. A bipolar recording technique (electrodes Oo-Po) was used, the negativity of the electrode Oo resulting in an upward deflection of the record. After recording the response, 0.34 - 0.57 mg/kg. of Largactil were given intravenously to each person examined and the responses were recorded again at intervals of 10, 20, 35 and

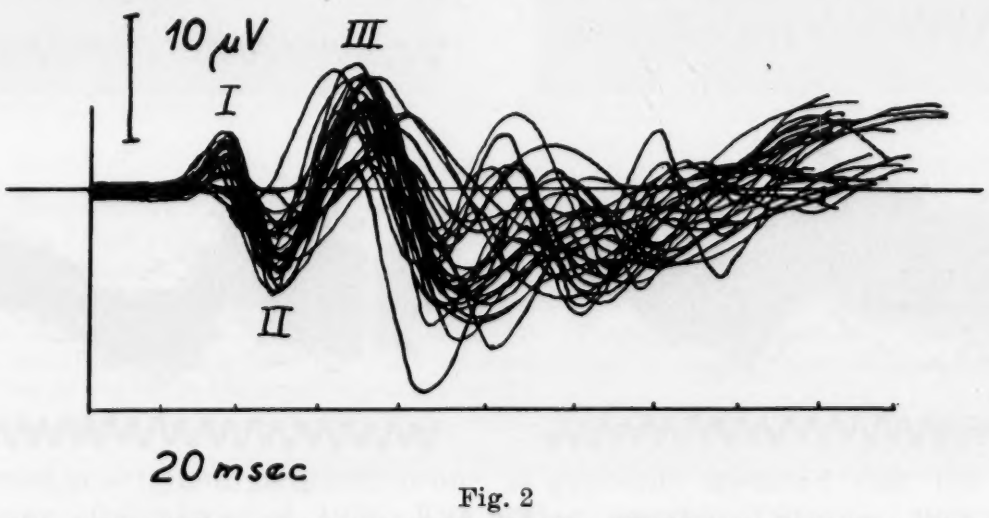

Fig. 2

The human EEG response to light stimulus (flash). Superposed tracings of 31 persons. The first three waves (I-III) are strikingly uniform, the remaining part of the response shows great inter-individual differences.

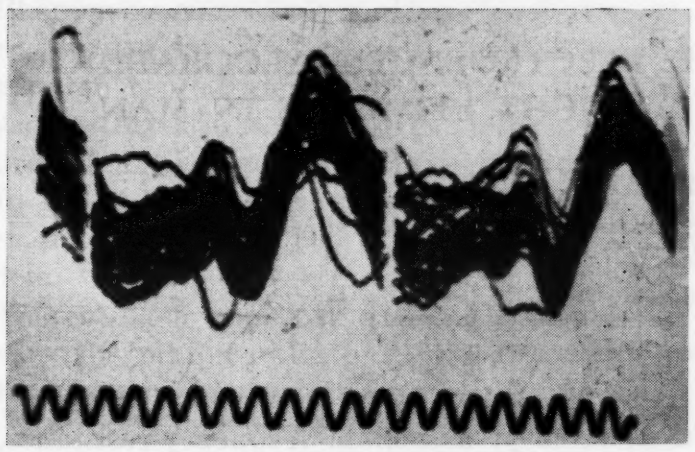

Fig. 3
The human EEG response to a light stimulus (flash). The rates of stimulus repetition: 10 per sec. The waves I-III remain unaltered at these rates, their amplitude even rises. Calib.: 10 msec., 5 μV.

50 min. Ten adult persons without cerebral damage and with normal EEG tracings were examined in this way.

RESULTS

In all persons under Largactil medication typical symptoms were observed: inhibition of psychomotor activity, loss of interest (Terzian 1954) and light sleep with possibility of momentary awakening. These symptoms reached their height in 35 min. In spite of this state the waves I-III of the response remained unchanged throughout all stages of the experiment (fig. 4), although there were often signs of sleep in the EEG tracings (fig. 5). In the part of the response following wave III no typical changes were observed after Largactil.

The following conclusions can be drawn from our results:

1. Largactil in doses such as stated above has no effect on the specific (visual) afferent system including the primary receiving area of the cortex.

2. The clinical and electroencephalographic effects of this drug must be attributed to its action on some other than the specific afferent system.

DISCUSSION

It is generally acknowledged that the effects of Largactil can be attributed largely to its action on the reticular activating system (Agafonov 1956; Anochin 1957; Bonvallet *et al.*, 1954; Bradley and Hance 1957; Galathea *et al.* 1956; Grenell *et al.* 1955;

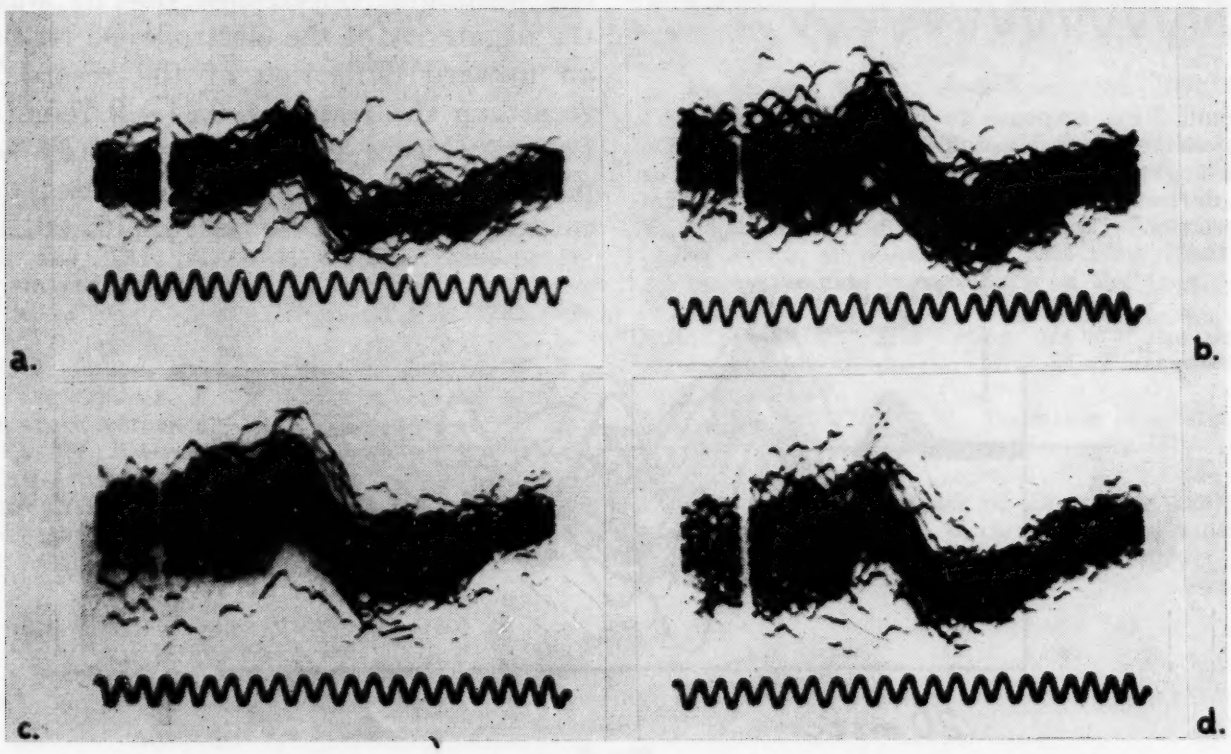

Fig. 4
The effect of Largactil on the EEG response to light stimulus (flash):
a. before Largactil
b. 10 min. c./ 20 min. d./ 45 min. after Largactil
The response remains unaltered. Calib.: 10 msec., 5 μV.

Hiebel *et al.* 1954; Ingvar and Soderberg 1957; Lehnmann and Hanrahan 1954; Stewart 1957; Terzian 1952, 1954; Terzian and Rubert 1954; Terzian 1955; Turner and Bérard 1954; Turner *et al.* 1956; Werner 1956). There are only a few who favor a hypothesis, ternuncial neurones of the spinal cord (Baryšnikov *et al.* 1956).

In the present experiments carried out on waking adults we have never observed any EEG response, which could be interpreted as mediated by some diffuse afferent system. It

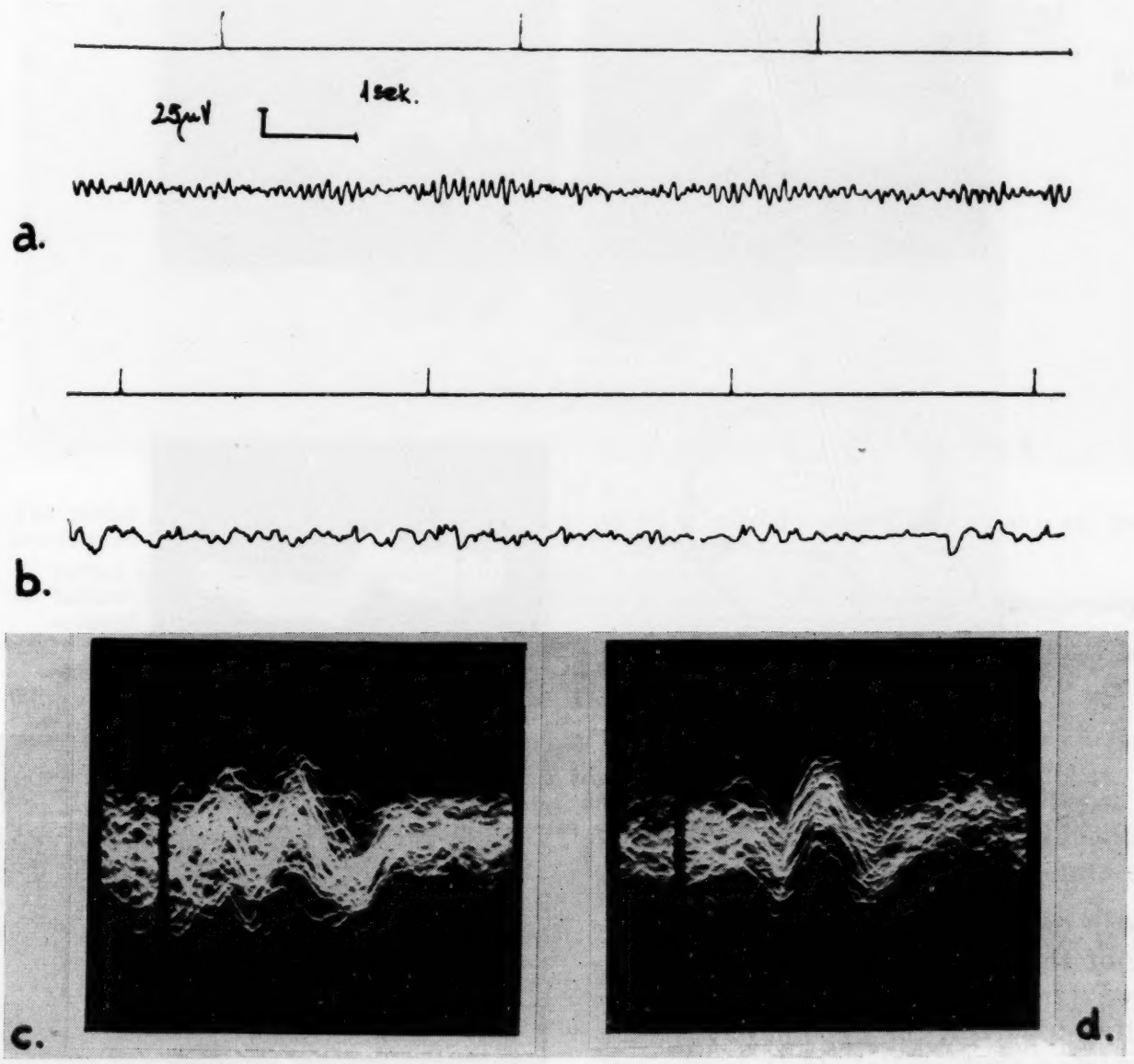

Fig. 5

Effect of Largactil on the EEG tracing (electrodes Oo-Po) and on the EEG response to a light stimulus (flash):

a. EEG tracing before Largactil. b. EEG tracing 30 min. after Largactil. c. EEG response before Largactil. d. EEG response 30 min. after Largactil.

Above the EEG tracings record from photo-cell. This figure shows the great value of Dawson's technique for detecting the EEG response which is imperceptible in the EEG tracing although clearly visible in the superimposed record.

that the predominant action of Largactil is on the cerebral cortex (Galenko *et al.* 1956; Kaminskij and Savčuk 1956), on thalamocortical circuits (Das *et al.* 1955; Werner 1956), on the hypothalamus (Sumulina 1956), or on in- is generally assumed that the general muscular reaction (Strauss 1928; Landis and Hunt 1939) is mediated by such pathways. The artefact produced by the blink component of the muscular startle reaction (Larsson

1956; Zang Z. Zao 1953) can be recorded over the frontal area by the technique of Dawson even in cases where it remains unobservable in the EEG tracing (fig. 6, 7). The amplitude of this artefact is considerably reduced both after Largactil and after a slight

3. The outstanding depressive action of Largactil on the blink component of the muscular startle reaction, with other results described, supports indirectly the hypothesis that Largactil exerts a preferential effect on the reticular activating system.

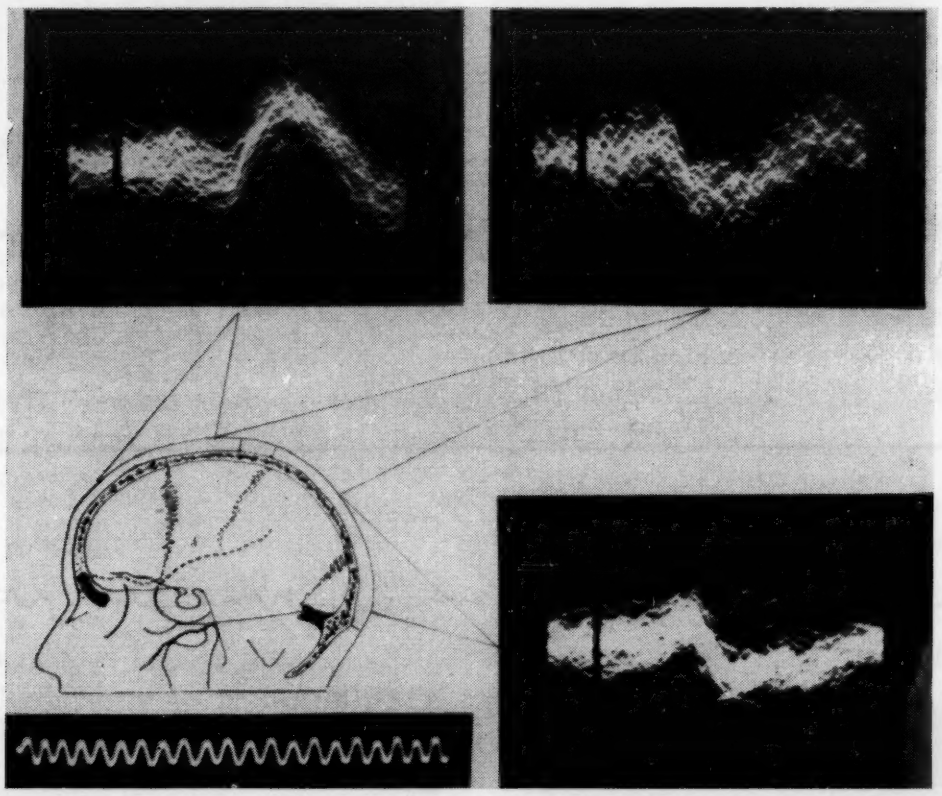

Fig. 6

The human EEG response to a light stimulus (flash) over the occipital area and the artefact of the blink component of the muscular startle reaction over the frontal area. The rates of stimulus repetition: 1 per 3 sec. Calib.: 10 msec., 5 μV.

increase in the frequency of stimulation while the size of the visual EEG response remains unaltered (fig. 8, 9). All these results are indirectly supporting the hypothesis that Largactil exerts a preferential effect on the reticular activating system.

SUMMARY

The effect of Largactil on the primary specific EEG response to light stimulation in man has been investigated. The findings and conclusions of the study are as follows:

1. Largactil has no effect on the specific (visual) afferent system.

2. The clinical and electroencephalographic effects of Largactil must be attributed to its action on some other than the specific afferent system.

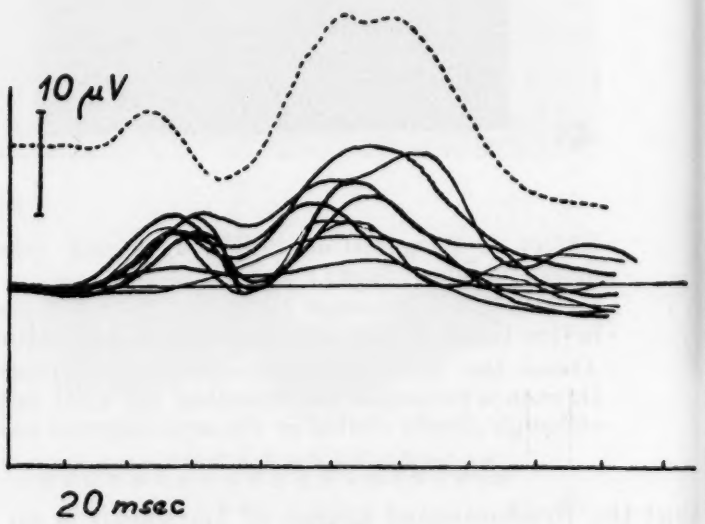

Fig. 7

The artefact of the blink component of the muscular startle reaction. Electrodes Co-Fo. The negativity of the electrode Fo results in an downward deflection of the record. Superimposed tracings of 10 persons.

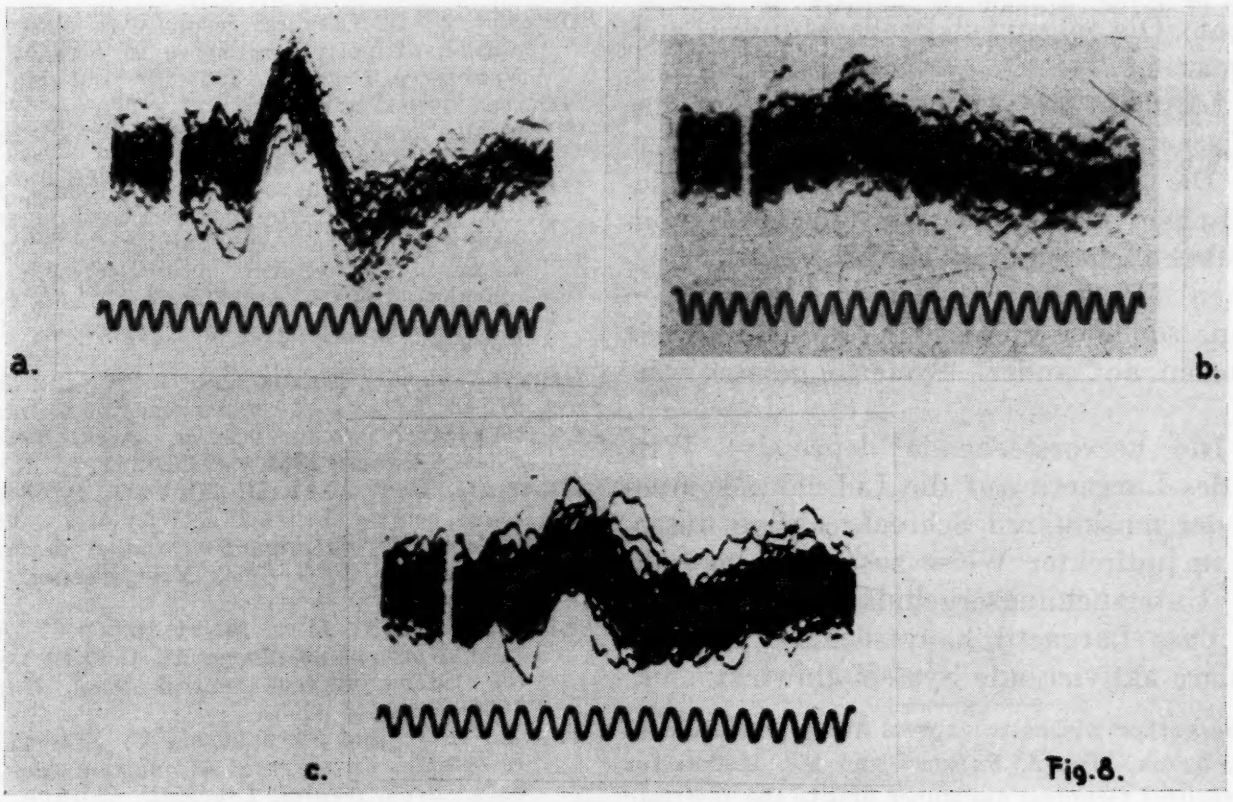

Fig. 8

The effect of Largactil and of increasing the rates of stimulus repetition (flash) on the artefact of the blink component of the muscular startle reaction:

a. before Largactil. Rates of stimulus repetition: 1 per 3 sec.
b. before Largactil. Rates of stimulus repetition: 2 per sec. The amplitude is considerably reduced.
c. 30 minutes after Largactil. Rates of stimulus repetition: 1 per 3 sec. The amplitude is considerably reduced.

Calib.: 20 msec., 5 μV.

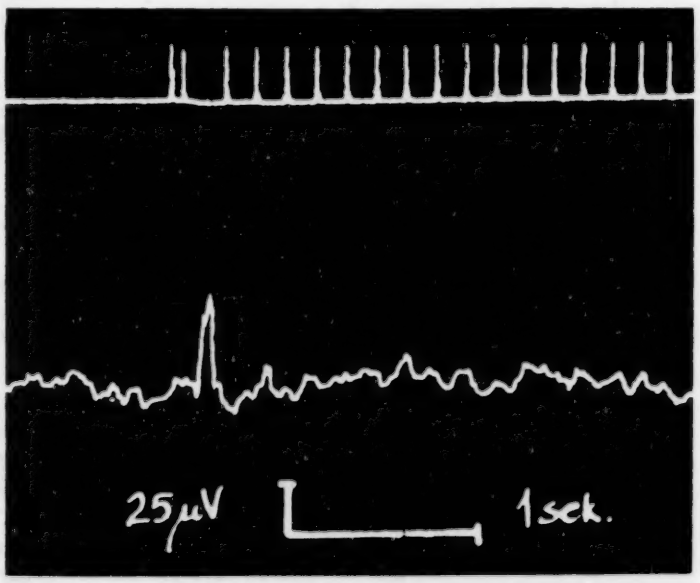

Fig. 9

The effect of increasing the rates of stimulus repetition (flash) on blink component of the muscular startle reaction. Electrodes Co-Fo. The negativity of the electrode Fo results on downward deflection of the record. Above the EEG tracing the record from the photo-cell. There is the response on the first stimulus only, the following responses are inperceptible in the EEG tracing but they are detectable by Dawson's superimposition technique.

RÉSUMÉ

L'effet du Largactil sur la réponse visuelle primaire à une stimulation lumineuse a été examiné chez l'homme. Les résultats et les conclusions sont:

1. Le Largactil n'influence pas le système afférent spécifique (visuel).

2. Les effets cliniques et électroencéphalographiques du Largactil doivent être attribués à une action autre que sur le système afférent spécifique.

3. L'action dépressive très marquée du Largactil sur l'artéfact produit par le clignement des yeux (considéré comme une partie de la réaction musculaire de sursaut), et les autres résultats décrits sont en faveur de l'hypothèse que le Largactil a un effet préférentiel sur la formation réticulée activatrice.

ZUSAMMENFASSUNG

Die Wirkung von Largactil auf die durch Lichtreiz hervorgerufene, primäre, spezifische EEG-Reizantwort beim Menschen wurde un-

tersucht. Die folgenden Beobachtungen wurden gemacht:

1. Largactil übt keine Wirkung auf das spezifische (visuelle) afferente System aus.

2. Die klinischen und elektroenzephalographischen Wirkungen des Largactils können daher nicht einer Beeinflussung der spezifischen afferenten Systeme zugeschrieben werden, sondern müssen in Beziehung mit Einflüssen auf andere Systeme gesetzt werden.

3. Die hervorstechende depressive Wirkung des Largactil auf die Lidschlusskomponente der muskulären Schreckreaktion unterstützt in indirekter Weise zusammen mit anderen Untersuchungsergebnissen die Hypothese, dass Largactil hauptsächlich auf das retikuläre aktivierende System einwirkt.

The author wishes to express his appreciation to Ing. J. Žalčík, Mrs. Z. Pafková and Mr. Hallon for their excellent technical assistance and to the Institute of Medical Photography and Film for their careful photography.

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THE ELECTROENCEPHALOGRAM IN KWASHIORKOR [1]

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(Received for publication: May 27, 1958)

The possibility of EEG disturbance in kwashiorkor (infantile protein malnutrition) was suggested by the profound apathy and irritability encountered in the disease (Clark 1951; Geber and Dean 1956). Evidence of organic brain damage in kwashiorkor is as yet confined to post-mortem findings consistent with cerebral oedema (Trowell *et al.* 1954).

In 10 cases Sarrouy *et al.* (1953) found greatly diminished voltage and frequency of brain potentials, lack of response to photic stimulation, and lack of change with the onset of sleep; in particular, the "characteristic fast activity of sleep" did not appear. These features were held to imply a decrease in cortical metabolic activity, and showed a tendency to disappear during recovery, although often persisting for up to three months afterwards. Their final disappearance was claimed to be the best criterion of complete recovery.

Engel (1956) found grossly abnormal EEGs in 7 fatal cases of kwashiorkor, due to the presence of excessive slow activity. The EEG was mildly to moderately abnormal in 16 cases which recovered. In the latter group, the EEG abnormalities disappeared during recovery, this trend being particularly rapid in a further 2 cases of mild kwashiorkor.

Engel concluded that the function of the cerebral cortex was impaired in the disease and that, although the EEG abnormalities appeared to have no prognostic value, the possibility of permanent brain damage was raised.

MATERIAL

The clinical subjects were 33 young African children suffering from moderate to severe kwashiorkor. Twelve were undergoing treatment at Baragwanath Hospital, Johannesburg, and 21 at the Unit of the Infantile Malnutrition Group of the British Medical Research Council, and at Mulago Hospital, the latter two in Kampala, Uganda. There were 19 males and 14 females. The mean age on admission was 20.70 (s.d. 8.69) months and the age range 8 to 44 months. Twelve children were anaemic (Hb $<$ 60 per cent) on admission to hospital, and 4 became anaemic later. Of the 33 cases, 26 recovered, 5 were removed from hospital by their parents before recovery was complete, and 2 died. In addition to these 33 patients there were 14 cases from whom single EEGs were recorded on admission to hospital. The age range was 11 to 59 months, mean 20.64 (s.d. 11.74).

The first control group comprised 11 African children (mainly surgical cases) from Baragwanath Hospital, from each of whom at least 2 serial EEGs were obtained. These children were selected as controls because they were not suffering from a debilitating disease, their nutritional status and mental state were both satisfactory, and their environment was similar to that of the kwashiorkor patients. The age range was 3 to 51 months, mean 31.0 (s.d. 17.1).

The second control group comprised 27 African children from whom single EEGs were obtained. There were 23 normal children and 4 convalescent surgical patients. The age range was 2 to 49 months, mean 12.9 (s.d. 10.9).

There were thus 47 kwashiorkor patients and 38 control subjects in all.

METHOD

Recording technique: EEGs were recorded by means of a 4-channel portable Ediswan electroencephalograph. In general, 11 electrodes in 7 different arrays were employed,

[1] This investigation was financed by the South African Council for Scientific and Industrial Research, and by a grant from the Mental Health Section of the World Health Organization, Geneva.

giving transverse and longitudinal bipolar derivations from the frontal, parietal, occipital and temporal areas.

Sedation was avoided because of the possible intrusion of fast activity into the EEG. However, the subjects frequently fell asleep during the recording session and occasionally even while the electrodes were being attached.

In the clinical group, the first EEG was obtained as soon as possible after admission to hospital, generally on the first or second day. Subsequent recordings were made at intervals of one week or more, depending on clinical progress. In isolated cases, EEGs were taken at daily intervals. Each patient had a minimum of 2 EEGs and several had 3 or more records, making a total of 94 EEGs from the 33 cases.

Photic stimulation was incorporated where possible. Notes were kept throughout the recording of any psychological changes.

In the serial control group, EEGs were obtained at intervals of one week to 3 months.

INTERPRETATION

(*a*) *Criteria of abnormality.*

In the absence of EEG frequency norms for African children, records were only classified as abnormal if they contained focal discharges.

(*b*) *Criteria of EEG "improvement".*

To enable detailed comparison of serial records, each distinguishable frequency component was individually assessed: if present for up to 25 per cent of the total waking record, it was assigned a rating of 1, and ratings of 2-4 represented the presence of a component for 26-50 per cent, 51-75 per cent and 76-100 per cent, respectively, of the waking record. The dominant EEG frequency was computed by taking the mean of all components with a rating of 2 or higher. The following criteria were adopted for the purpose of assessing EEG "improvement":

(i) Disappearance of abnormality, if any.
(ii) Increase in dominant frequency.
(iii) Appearance of, or increase in, response to photic stimulation.
(iv) Appearance of, or increase in, fast activity, especially spindles, during sleep.

(*c*) *Assessment of mental state.*

The following criteria were adopted in assessing improvement in mental state in the clinical group:

(i) Alleviation of misery, apathy and irritability.
(ii) Increase in euphoria, interest in toys, etc., and co-operation with the tester.

TABLE I

INCIDENCE OF ABNORMAL RECORDS IN 47 KWASHIORKOR PATIENTS ON ADMISSION TO HOSPITAL, AND 38 CONTROLS; WAKING AND SLEEPING EGGs

State	Patients on admission			Controls			Sig. of difference
	Available records	No. abnormal	%	Available records	No. abnormal	%	
Waking	41	5	12	35	0	0	$p < .02$ (sig.)
Sleeping	24	10	42	13	1	8	$p < .01$ (sig.)
Sig. of difference	$p < .02$ (sig.)			$p > .05$ (not sig.)			

RESULTS

(*a*) *EEG abnormalities.*

In the clinical group, 9 of the 33 cases (27 per cent) had abnormal EEGs on admission to hospital. In 4 of these the abnormalities were not present in the second EEG. As a rule EEG abnormalities were present during

only one phase of the recording (i.e. awake, or asleep) and both these phases were not represented in all the EEGs taken, so that definite evidence of the disappearance or persistence of foci was not available in 5 of the above 9 cases. Six children of these 9 had a third EEG, the record remaining normal in one, being again abnormal in 3 and comparison being impossible in 2. Thus the abnormalities present on admission to hospital disappeared in only 2 patients out of 9 and disappeared temporarily in 3 cases. In one case the abnormality reappeared in a different state of consciousness. Only one of these patients was anaemic on admission. All but one recovered; the latter developed anaemia at the time of the 2nd EEG and died 3 days later.

Four cases had normal EEGs on admission but later records were abnormal. One of these cases was anaemic on admission and another had developed anaemia at the time of the last EEG. All four recovered.

There were 4 abnormal records amongst the 14 patients with single EEGs. None of

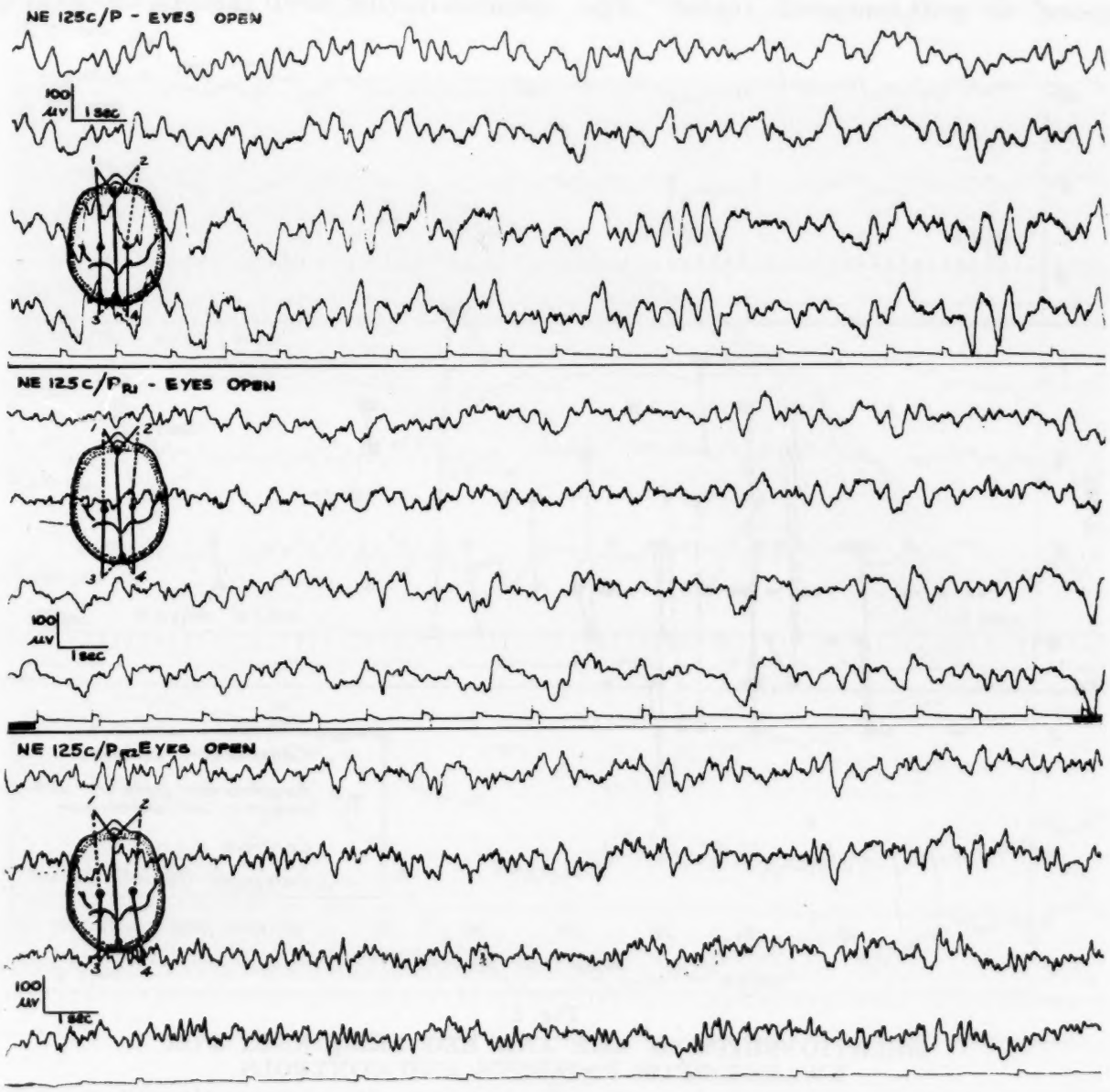


Fig. 1

INCREASE IN EEG FREQUENCY DURING RECOVERY FROM KWASHIORKOR

Case 29: serial EEGs, female Ganda, 18 months, awake, kwashiorkor with anaemia. Clear increase in dominant frequency. Top tracing on admission, 2nd tracing 7 days later and 3rd tracing after a further 7 days. Clinical recovery complete, discharged 6 days after 3rd EEG. *Note*: In the lowest sample there is a fault in the time-marker trace, rendering every other "pip" indistinct.

these cases was anaemic at the time of the EEG and all recovered from kwashiorkor.

Thus, of a total of 47 kwashiorkor patients, 13 (28 per cent) had abnormal records on admission to hospital. All but one of these abnormalities were in the form of focal disturbances at theta and/or delta frequencies in the temporal or post-temporal region. The abnormal record, in the form of a delta focus in the left temporal region.

The incidence of abnormality in waking and sleeping records for patients and controls is summarized in table I. The patients had significantly more abnormalities in both states, and also significantly more abnormal records during sleep than in the waking state.

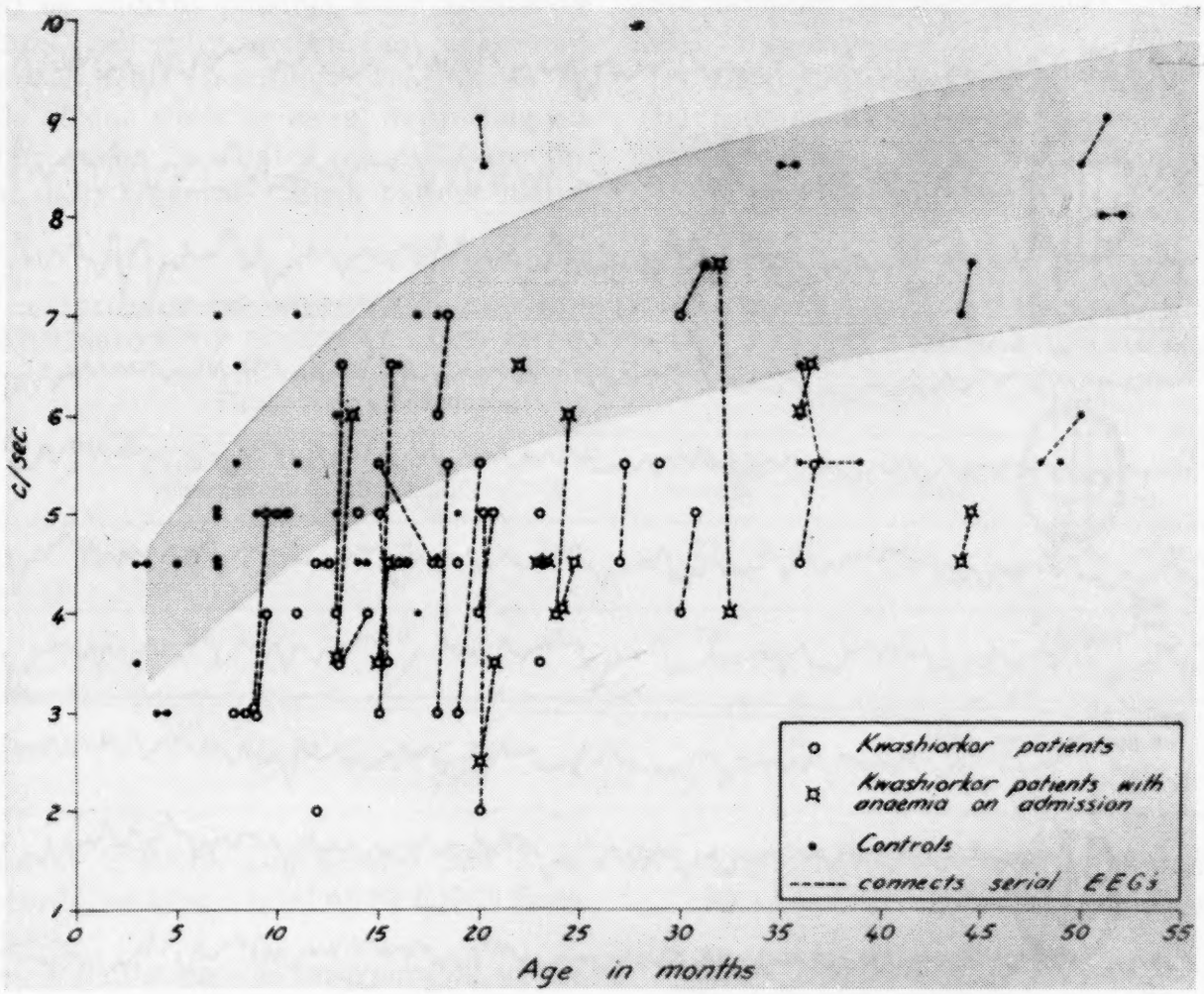


Fig. 2
RELATIONSHIPS OF AGE AND EEG FREQUENCY FOR KWASHIORKOR PATIENTS AND CONTROLS

Dominant EEG frequency in relation to age for 38 kwashiorkor patients (10 with anaemia), 11 control children with serial EEGs and 24 controls with single EEGs. Changes in frequency over short periods are indicated. The shaded area indicates approximately the range of Lindsley's data for 132 normal American children (1939).

remaining abnormality was a slow wave focus in the parietal area. Total incidence of abnormality, including abnormalities seen in subsequent records, was 36 per cent.

In the serial control group ($n = 11$) there were no abnormal EEGs. Only one of the 27 control subjects with single EEGs had an

(*b*) *Changes in dominant frequency.*

There were 28 patients with serial waking EEGs. The mean frequency of dominant activity on admission was 4.11 (s.d. 1.18) c/sec., and at the time of the final EEG, 4.98 (s.d. 0.98) c/sec., this difference being statistically significant ($p < .01$). Dominant frequency

was accelerated in 21 cases, unchanged in 4, and decelerated in 3 cases.

Nine of these patients had anaemia on admission. Those without anaemia had a lower mean frequency on admission, (3.95, s.d. 1.01 c/sec.) and a higher mean frequency at the last EEG (5.00, s.d. 0.99 c/sec.) than did the anaemia group (4.44, s.d. 1.44 and 4.94, s.d. 0.96), but these differences were not statistically significant.

Of all the above 28 cases, 23 recovered from kwashiorkor, 4 were removed from hospital before recovery was complete, and one deteriorated. Clinical improvement was accompanied by an increase in dominant frequency in 22 cases (e.g. fig. 1), by no change in frequency in 3, and by a decrease in frequency in three. In the case which deteriorated, there was a decrease in frequency.

For all 28 cases, there was a highly significant negative correlation of mean dominant frequency on admission with change in frequency from the first to the last EEG ($r = .655$, $p < .001$). This suggested that there was

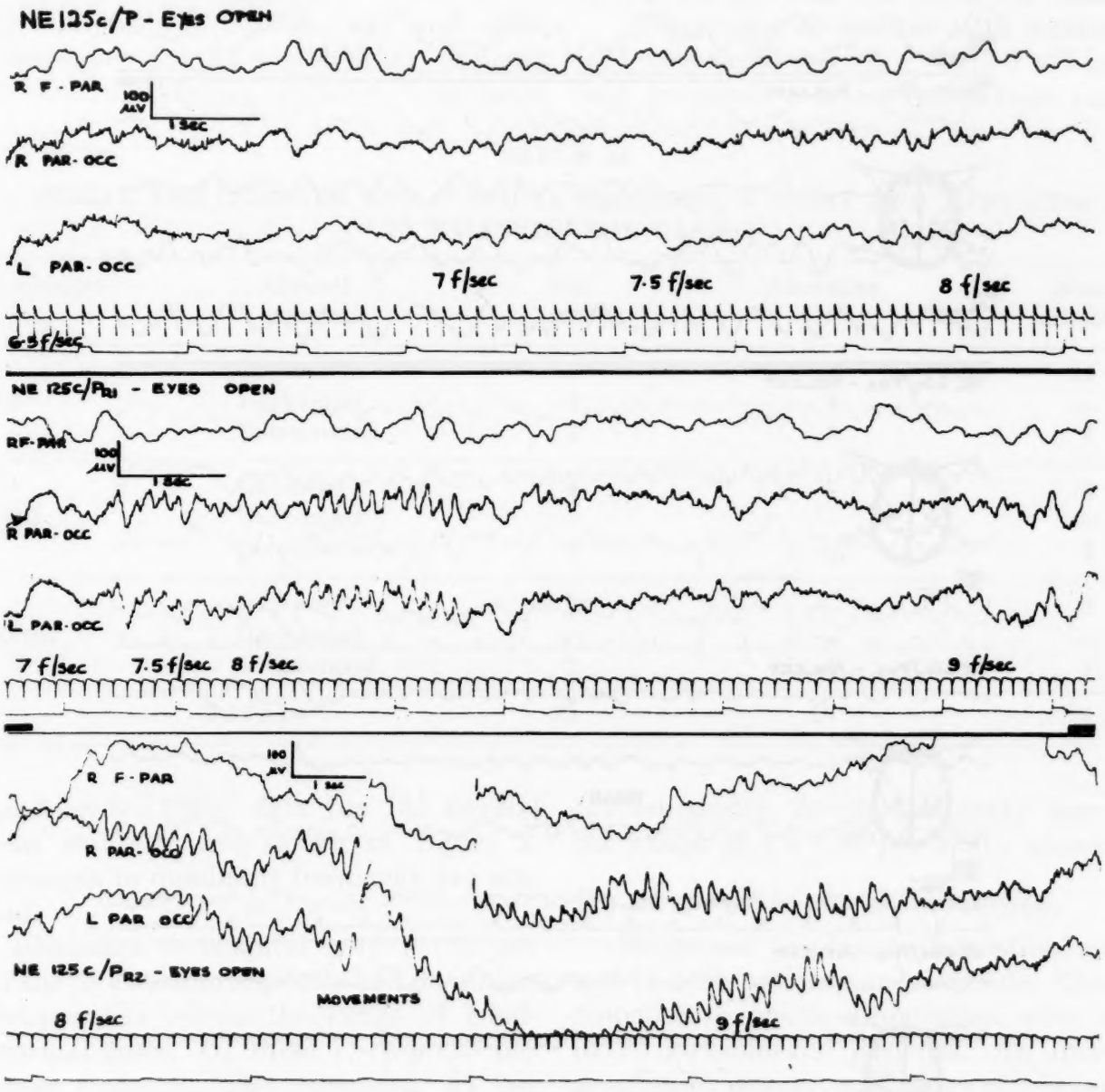
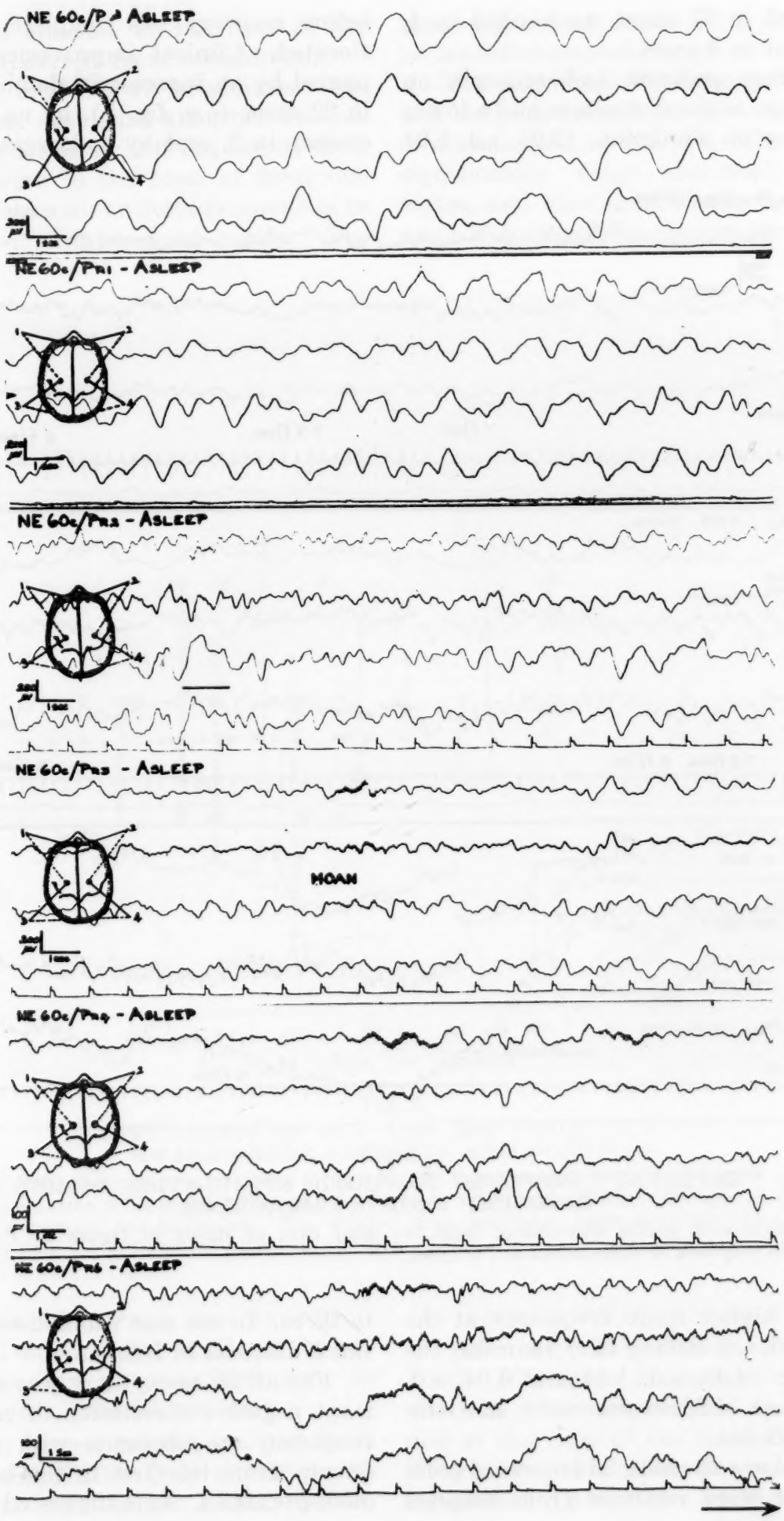


Fig. 3
"IMPROVED" RESPONSE TO PHOTIC STIMULATION DURING RECOVERY FROM KWASHIORKOR

Serial EEGs with photic stimulation from the same case as shown in figure 1. Progressive increase in response to stimulation at 7-9 f/sec.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NE 60c/PR5 - ASLEEP

a greater increment in frequency in those cases with lower dominant frequencies on admission to hospital.

In the serial "normal" group there was an increase in frequency in 3 children, no change in 6 and a decrease in 2.

The relationships between age and dominant frequency for 37 kwashiorkor patients and 33 control African children, compared with Lindsley's (1939) data for 132 normal American children, are shown in figure 2. Serial changes in dominant frequency are also indicated.

On admission to hospital only 7 (18 per cent) of the 38 kwashiorkor cases had dominant EEG frequencies within the range of Lindsley's normal cases. Of these 7, two (29 per cent) were anaemic. The remaining 31 patients all had frequencies below this range, 8 (26 per cent) of these being anaemic.

At the final EEG only 11 (39 per cent) of the 28 patients with serial waking EEGs had frequencies within the normal range. Three of these (27 per cent) were anaemic. The remaining 17 all had frequencies below the range and 6 (35 per cent) of these were anaemic.

There were 33 controls with waking EEGs (11 with serial records). Only 9 (27 per cent) had frequencies below the normal range. Of the remainder, 20 (61 per cent) were within the range and 4 (12 per cent) above it.

TABLE II

SERIAL EEG CHANGES AND CLINICAL PROGRESS — FIRST AND LAST EEGs
33 KWASHIORKOR CASES

EEG changes	Clinical changes	All cases	Anaemias	Non-anaemias
Improved	Improved	21	7	14
	Unchanged	1	1	—
	Deteriorated	2	1	1
Unchanged	Improved	4	—	4
	Unchanged	—	—	—
	Deteriorated	1	—	1
Deteriorated	Improved	2	—	2
	Unchanged	—	—	—
	Deteriorated	2	1	1
	TOTALS :	33	10	23

(*c*) *Response to photic stimulation.*

Responses to photic stimulation were normal in both patients and controls. Changes in response to photic stimulation were assessed in 22 kwashiorkor patients. An increase in amplitude, amount and range of responses was shown in 15 cases (e.g. fig. 3), a decrease in 2 and no change in 5. Of the 22 patients, 20

Fig. 4

INCREASE IN EEG FREQUENCY IN SLEEP DURING RECOVERY FROM KWASHIORKOR

Case 13: male Ganda aged 13 months, kwashiorkor. Serial EEGs recorded during sleep on the 1st, 3rd, 4th, 5th, 6th and 18th days after admission. Dominant frequency increases from 0.5 to 1 c/sec. (top sample) to 3-4 c/sec. (last sample). Spindles of fast activity appear in the EEG on the 4th day and are clear the next day. There is a sharp wave focus in the right temporal region on the 4th, 5th and 6th days (underlined in the third sample, not apparent in the fourth).
Note: The mechanical fault in the time-marker trace seen in figure 1 is also present in the first two samples in this figure.

improved clinically and 2 deteriorated. Clinical improvement was accompanied by an improved response in 15 cases, by no change in 4, and by a deterioration in response in one.

(*d*) *Changes in the EEGs during sleep.*

Only 4 cases had sleeping records on both the first and final occasions, 3 of these showing no change and one deterioration in the

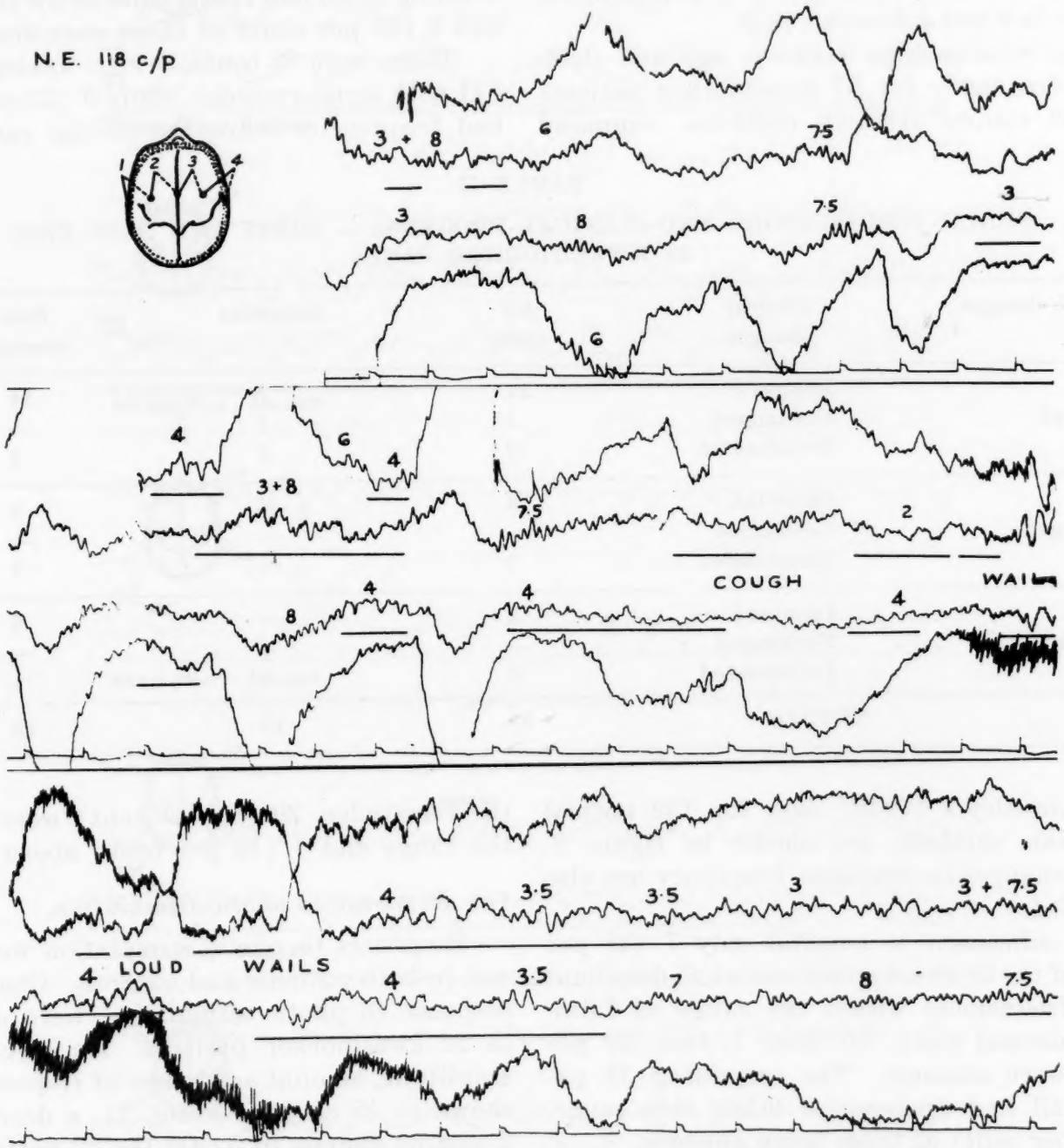

Fig. 5

EEG CONCOMITANTS OF AFFECTIVE CHANGE

Case 47: male Ganda, 22 months, kwashiorkor; awake with eyes open. Initially rhythms from 6-8 c/sec. are predominant. With increasing distress, theta and slower rhythms, greater on the left side, become dominant. These slow waves are sometimes co-existent with "alpha" rhythms and hence represent intrusion of a new component.

The patient who deteriorated clinically had a deteriorated response.

In the serial normal group, 3 showed improved responses, 6 were unchanged, and in 2 cases no assessment could be made.

pattern. These patients all improved clinically. One further case (fig. 4) showed an improved sleeping EEG pattern during recovery, but did not sleep on the final occasion. Spindle activity was seen in 15 (63 per cent)

of the patients on admission (n = 24) and 16 (84 per cent) of the controls (n = 19), this difference being insignificant.

(*e*) *EEG "improvement".*

Of the 33 kwashiorkor patients with serial EEGs, the final records were "improved" in 24 cases, "deteriorated" in 4 and "unchanged" in 5 cases. The relationship between these assessments and clinical changes is shown in table II. In 27 clinically improved cases, 21 had "improved" EEGs 4 had "unchanged" and 2 "deteriorated" records.

Only one case of the 5 which deteriorated clinically during the EEG series failed to recover, this being the patient who died of anaemia, mentioned earlier. The only other fatal case was recovering from kwashiorkor at the time of the last EEG, but contracted pneumonia 9 days later, dying within 24 hours of diagnosis, probably due to penicillin allergy.

CHANGES IN MENTAL STATE

Assessment of mental change was possible in 24 cases. In 14 (58 per cent) there was improvement, 12 with concomitant EEG "improvement" and 2 with no EEG change. In 9 patients (38 per cent) there was no marked change in mental state, 6 of these showing EEG "improvement", the remainder showing no EEG change. Deterioration in mental state occurred in one patient (a fatal case) and was accompanied by EEG "deterioration".

In addition to these general relationships, transient affective changes were often accompanied by augmentation of theta and slower rhythms. A typical instance in which these EEG changes accompanied increasing distress is illustrated in figure 5.

DISCUSSION

The high incidence of focal abnormalities in the temporal lobe in this group of kwashiorkor patients is striking and has not been previously reported in the disease. There is an apparently significant relationship between the abnormalities in these patients and their level of consciousness, the incidence of foci being greater in sleep than during the waking state. It is possible that these foci represent the localization to this area of some feature such as cortical oedema (cf. Walter 1937) or that the temporal lobe is peculiarly vulnerable to the gross physiological disturbances in kwashiorkor. Strauss *et al.* (1955) suggested that focal slow activity in the temporal region appears sooner and often in greater degree than abnormality elsewhere in the presence of disease in almost any part of the cerebral hemisphere. However, Corbin and Bickford (1956) suggested that the clinical significance of focal abnormalities in young children is much lower than in adults, owing to the relatively high incidence of such foci in normal children. The present study does not corroborate this contention, since only one of 38 normal children had a focal abnormality.

An unequivocal finding is that the alleviation of the physical and mental symptoms of kwashiorkor is usually accompanied by an "improvement" in the EEG, implying acceleration of dominant frequency, and an increased responsiveness to photic stimulation. In regard to the frequency of the EEG in particular, changes occur during recovery from the disease which are greater than those normally to be expected as a result of maturation over short intervals, and clearly in excess of those found in control subjects. Furthermore the majority of the patients had a dominant EEG frequency below the range of Lindsley's group and of the controls, even at the last EEG. These findings raise the possibility that kwashiorkor exerts an impeding effect on the development of brain rhythms in childhood and that recovery from the disease is paralleled by a partial removal of this effect. This supports the hypothesis of Gallais *et al.* (1951b) and Mundy-Castle *et al.* (1953) that the high incidence of EEG abnormalities in a group of normal West African Negro adults (Gallais *et al.* 1951 a and b) might be at least partially the result of endemic diseases such as kwashiorkor.

There appear to be a number of specific factors which might be responsible for the present findings: Engel (1956) suggested that anoxic effects on the brain resulting from anaemia in kwashiorkor might be reflected in the EEG. In the present study no significant

difference was found between the mean dominant frequency of the anaemia and non-anaemia groups, either on admission or at the last EEG, and only one of the 9 patients with abnormal EEG's on admission to hospital had anaemia at the time. Furthermore, the EEG consistently "improved" in 3 out of 4 patients who developed anaemia during treatment, "deteriorating" in only one child, who died of anaemia. One further case had EEG "improvement", in spite of increasing anaemia, up to his removal from hospital. It therefore appears that anaemia is not a critical factor.

There appears to be no relationship between the retardation of EEG frequency in kwashiorkor and basal metabolic rate. A decrease in alpha frequency in adults accompanies lowering of the BMR (Lindsley and Rubinstein 1939), but the BMR in kwashiorkor is probably raised except in very severe cases (Dean 1957).

The dysphoria, irritability and reduced motility of children with kwashiorkor may contribute to the EEG changes. The tendency of the mental state of kwashiorkor patients to improve with clinical recovery is no doubt reinforced by greater relaxation following on increasing familiarity with the EEG recording situation. Since the rhythms of childhood often respond in a similar way to the alpha rhythms of the adult, this tendency would lead to an increase of faster rhythms, due to augmentation of alpha or alpha-like activity. Furthermore, slow waves were often augmented during periods of acute distress. Similar findings have been reported in children and adults (Hoagland *et al.* 1938; Hill 1950; Walter 1950; Mundy-Castle 1951, 1957; Klackenberg and Melin 1953). The EEG changes during recovery from kwashiorkor may therefore be influenced by such psychological factors.

The results of this investigation differ in two main respects from those of previous studies: (*a*) the high incidence of temporal lobe abnormalities; and (*b*) the presence of fast activity in sleep during the acute phase of the disease.

SUMMARY

1. Serial EEGs were recorded from 33 young African kwashiorkor patients, 10 of whom were anaemic. Serial EEGs were also obtained from 11 control children and single recordings from a further 14 kwashiorkor patients and 27 controls.

2. Abnormal (focal) records were found in 36 per cent of the kwashiorkor patients, all except one in the form of disturbances in the temporal region. Most of the abnormalities were seen in sleep records.

3. During recovery there was usually a marked increase in dominant EEG frequency and in response to photic stimulation. The dominant frequencies of the kwashiorkor children were mostly below the range for normal American children of the same age, even after clinical recovery. No comparable serial EEG changes occurred in the controls, and dominant frequencies were similar to those of normal American children.

4. The changes in dominant frequency during recovery might reflect an impeding effect of kwashiorkor on the development of brain rhythms in childhood. This effect may persist into adulthood.

5. Neither anaemia nor BMR appear to be responsible for the EEG changes, whereas psychological factors may be of significance.

RÉSUMÉ

1. On a enregistré à plusieurs reprises et d'une façon systématique l'électroencéphalogramme de 33 jeunes malades africains atteints de kwashiorkor (malnutrition protéinique infantile), et dont 10 présentaient de l'anémie. Il y avait en plus 11 enfants avec des électroencéphalogrammes de contrôle et des enregistrements uniques ont été obtenus chez 14 malades atteints de kwashiorkor et chez 27 sujets de contrôle.

2. On a trouvé chez 36 pour cent des malades des altérations électroencéphalographiques focales. Toutes ces perturbations étaient situées dans la région temporale, excepté chez un malade. La plupart des altérations électroencéphalographiques se manifestent pendant le sommeil.

3. Comme règle générale pendant le rétablissement il y avait une augmentation marquée de la fréquence électroencéphalographique dominante et de la réponse à la stimulation lumineuse. D'habitude les fréquences dominantes des enfants atteints de kwashiorkor étaient plus basses que les fréquences dominantes électroencéphalographiques des enfants américains du même groupe d'âge, même après la guérison clinique complète. Dans le groupe de contrôle, ces perturbations électroencéphalographiques ne se présentaient pas, et les fréquences dominantes étaient du même ordre que chez les enfants américains normaux.

4. Le changement de la fréquence dominante pendant le rétablissement pourrait indiquer une influence du kwashiorkor sur le développement des rythmes cérébraux de l'enfance. Cet effet pourrait persister plus tard.

5. Ni l'anémie ni les altérations du métabolisme basal semblent être responsable pour les anormalités électroencéphalographiques, tandis que des facteurs psychologiques pourraient avoir une signification.

ZUSAMMENFASSUNG

1. EEG-Untersuchungen wurden serienweise bei 33 jungen afrikanischen Patienten durchgeführt, welche an Kwashiorkor (infantile Proteinunterernährung) litten. 10 dieser Patienten waren anämisch. Serienweise EEG-Untersuchungen wurden ebenfalls bei 11 Kindern als Kontrolle ausgeführt und Einzel-EEG-Untersuchungen wurden aufgenommen bei 14 Patienten mit Kwashiorkor und bei 27 Kontollsubjekten.

2. Abnorme Kurvenbilder mit herdförmigen Veränderungen wurden in 36 Prozent der Kwashiorkor-Patienten gefunden. Die Störungen im Hirnstrombild erschienen alle, abgesehen von einem einzelnen Fall, in der Temporalregion. Die abnormen Veränderungen wurden am häufigsten in Schlaf-EEGs beobachtet.

3. Während der Heilung ereignete sich im allgemeinen eine deutliche Zunahme der dominanten EEG-Frequenzen und eine Verbesserung der Antworten auf intermittierende Lichtreize. Die dominanten Frequenzen bei Kindern mit Kwashiorkor lagen im allgemeinen unterhalb der Werte, welche für normale amerikanische Kinder derselben Alterstufe ermittelt worden waren. Dies galt sogar nach Eintreten klinischer Heilung. Keine derartigen EEG-Veränderungen wurden in den serienweisen EEG-Untersuchungen der Kontrollsubjekte gefunden, und die dominanten Frequenzen waren ähnlich denjenigen, welche für normale amerikanische Kinder beschrieben worden waren.

4. Veränderungen in der dominanten Frequenz während des Heilprozesses scheint möglicherweise der Ausdruck eines verzögernden Einflusses der Kwashiorkor-Erkrankung auf die normale Entwicklung der Gehirnrhythmen im Kindesalter zu sein. Es ist möglich, dass dieser verzögernde Effekt bis ins Erwachsenenalter anhält.

5. Weder die Anämie noch die Veränderungen des Grundumsatzes scheinen verantwortlich zu sein für die EEG-Veränderungen. Es ist jedoch möglich, dass psychologische Faktoren eine gewisse Bedeutung haben.

The author wishes to thank the following: Dr. R. F. A. Dean, Medical Research Council, Kampala, Uganda; Dr. E. Kahn and Dr. S. Wayburn, of Baragwanath Hospital, Johannesburg, for the facilities they placed at the author's disposal, and Dr. A. C. Mundy-Castle, National Institute for Personnel Research, for advice and criticism.

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PRINTED IN CANADA

THE DURATION OF HUMAN ELECTROENCEPHALOGRAPHIC AROUSAL RESPONSES ELICITED BY PHOTIC STIMULATION [1]

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(Received for publication: June 20, 1958)

The phenomenon of the desynchronization of the normal resting electrical activity of the brain in response to sensory stimulation has been the subject of many studies (Jasper *et al.* 1935; Loomis *et al.* 1935, 1936, 1938; Travis and Knott 1936, 1937; Jasper and Cruickshank 1936, 1937; Cruickshank 1937; Travis and Hall 1938; Bakes 1939; Knott and Hadley 1942; Knott *et al.* 1944). Most recently the demonstration of the mediation of this response by the reticular system (Moruzzi and Magoun 1949) has added further impetus to a study of the electroencephalographic alpha "blocking" which has been called arousal. Early studies of arousal were directed toward the determination of the latency of the response, and of the factors influencing the latency (Jasper *et al.* 1935; Jasper and Cruickshank 1936, 1937; Bagchi 1937; Cruickshank 1937; Travis and Hall 1938; Baker 1939). Some workers, notably Loomis *et al.* (1936), Knott and Hadley (1942), Travis and Knott (1936, 1937) and more recently, Darrow *et al.* (1957) have reported observations on the duration of the response. These latter workers have concerned themselves for the most part with the duration of responses to sound, although Loomis *et al.* (1936) and Travis and Knott (1936, 1937) did investigate the duration of responses to light.

Observations on arousal in central nervous system disturbances have revealed the usefulness of this response for clinical evaluation of patients (Grossman 1949; Li *et al.* 1952). Further, a comparison of the duration of arousal responses before and after the administration of drugs acting on the central nervous system has recently been carried out (Glotfelty and Wilson 1956; Wilson and Glotfelty 1958; Morrell). The significance of these studies is questionable, however, until investigations of the normal response curve have been made.

In two preliminary investigations it had been observed that arousal responses to sound and tactile stimuli (Glotfelty and Wilson 1956 and 1958) were quite variable and the durations and intensities of the stimuli were difficult to control. On the other hand, responses to single stroboscopic light flashes were quite consistent and the stimuli were easily controlled. As a result of these observations single photic flashes were used as the arousal stimulus. The present study is aimed at determining the response duration curve, and observing the effect of simultaneous sound stimuli and attention on the duration of the arousal response.

METHOD

Eighty physically and electroencephalographically normal males and females served as experimental subjects. These volunteers were university undergraduate, graduate, and medical students, as well as a small number of medical technicians and faculty. Ninety-two studies were carried out in these subjects.

All subjects had well developed and well regulated alpha rhythms which were present in the records for at least 50 per cent, and in the majority of cases, for more than 75 per cent of the period of recording.

[1] This work was supported by a grant (M 1203) National Institute of Mental Health.

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Electroencephalographic recordings were made using a Grass III D electroencephalograph. Chlorided silver disc electrodes were applied with collodion in standard frontal, central, parietal, occipital, mid-temporal, and central vertex placements. Bipolar electrode combinations were used.

With the subject recumbent, photic arousal responses were elicited using a Grass PS-1 photic stimulator. The light was placed about 8 inches from the subject's face. Single flashes of constant intensity were administered at 5 to 15 sec. intervals, the average interval for any one minute period being 10 sec. This random variation was done in order to prevent anticipation of the photic stimulus. Since many subjects tended to become drowsy, it was necessary to call to them when electroencephalographic evidence of drowsiness was observed.

The subjects were divided into six groups for investigation: group I, consisting of 17 subjects, was subjected to 5 min. of photic stimuli. A 20 min. rest period was allowed to elapse and a second series of photic stimuli was presented for a 5 min. period. Group II, consisting of 15 subjects, as did subsequent groups, was subjected to 5 min. of photic stimuli. During the 20 min. rest period a 7 min. tape recording consisting of an anecdote obtained from H. Allen Smith (1953) was played. A second 5 min. period of photic stimuli was then administered during which a second Smith anecdote was played.

Group III was administered 5 min. of photic stimuli, followed by a 20 min. rest period. A second 5 min. period of photic stimuli was presented, together with the second recording from group II. These subjects were instructed to remember the story, and were told that they were to retell the story after the experiment was terminated. Group IV was administered 5 min. of photic stimuli together with the second recording. Group V was presented with photic stimuli for 30 consecutive minutes, to determine whether extinction of the arousal responses would occur. Group VI was administered 5 min. of photic stimuli followed by a 20 minute rest period. The subjects then squeezed a rubber bulb in response to the light flashes in a second 5 min. period.

The parieto-occipital leads of the electroencephalographic recordings were selected for study of the duration of the arousal responses, as the alpha rhythms, and concomitantly their suppression, were best developed in these areas.

An arousal response was for the purposes of this study arbitrarily considered to be a suppression of alpha rhythm, following the photic stimulus at the end of a normal latency period, with at least a 50 per cent decrease in voltage and/or an increase of the frequency to more than the upper limit of alpha range (13/sec.). The responses were measured from the crest of the last complete alpha wave following the stimulus to the crest of the first of the next sequence of three or more alpha waves to reappear. These crest-to-crest distances were measured to the nearest 0.1 sec. A typical arousal response is shown in figure 1.

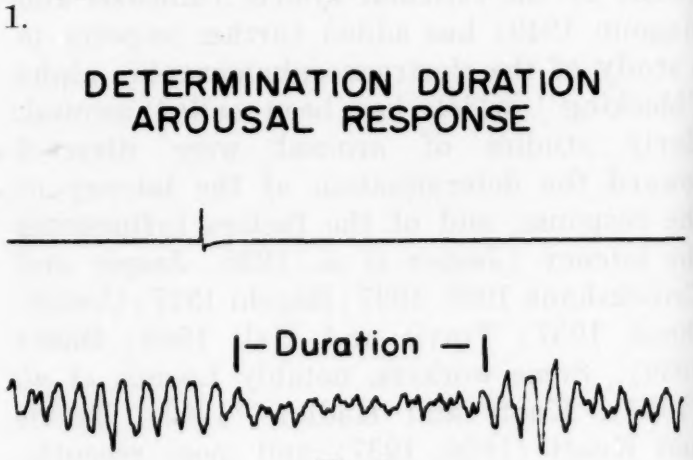

Fig. 1

The side of the head which showed, in the individual subject, the greatest voltage and/or frequency differential between the resting alpha rhythm and the arousal response was arbitrarily chosen in that subject. If the response on the chosen side was equivocal the response on the opposite side was then used. If neither response was measurable a zero response was recorded.

RESULTS

Since the stimuli were presented at random intervals but averaging every 10 sec., the responses obtained were grouped accordingly in 10 sec. periods. Mean values for each group

at 10 sec. intervals were then obtained. It was apparent that there was little change in the means of any 3 consecutive 10 sec. periods. Therefore for purposes of statistical analysis the data were grouped in 30 sec. periods.

The data of 77 studies from the first 5 min. of control recording of groups I, II, III, V, and VI, are presented together in tabular form in table I, and graphically in figure 2. The mean of the arousal responses for the first half minute of photic stimuli was 1.23 sec., and within 1 min. this had dropped to the .6 to .7 range it maintained throughout the rest of the 5 min. The standard deviations (SD) are given for these means.

TABLE I

Mean arousal response durations (in seconds) of 77 studies from the 5 min. of control recording of groups I, II, III, V and VI.

Minutes of recording	Arousal responses	Standard deviations
0 - .5	1.23	0.65
.5-1	0.90	0.53
1 -1.5	0.71	0.42
1.5-2	0.70	0.45
2 -2.5	0.68	0.46
2.5-3	0.66	0.46
3 -3.5	0.72	0.46
3.5-4	0.69	0.43
4 -4.5	0.61	0.35
4.5-5	0.60	0.40

Group V, which was presented light flashes for 30 consecutive minutes, was seen to start off as did the larger series above, with a mean of 1.16 sec. for the arousal responses in the first half minute, which rapidly dropped to the .55 to .6 sec. range. These

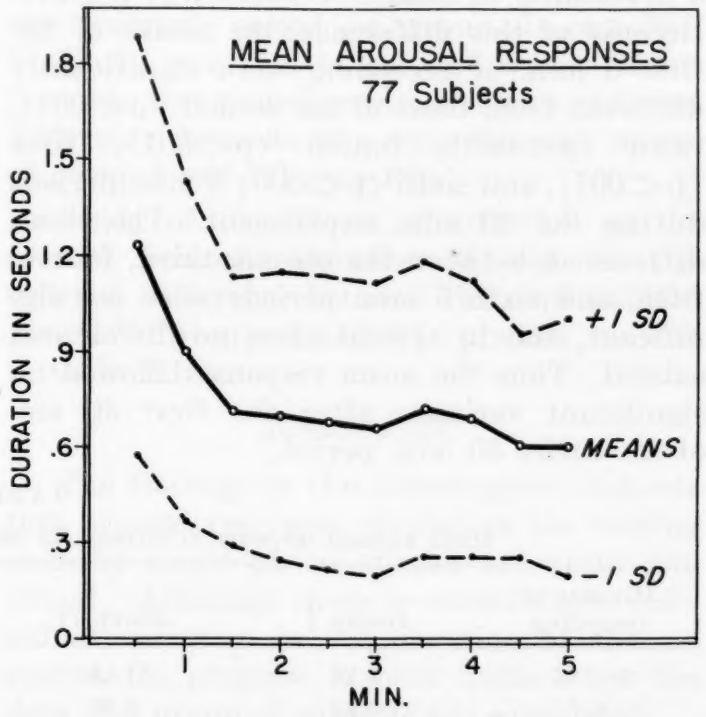

Fig. 2

TABLE II

Mean arousal response durations (in seconds) during 30 min. of consecutive recording (group V).

Minutes of recording	Arousal Responses in Minutes 0-5	5-10	10-15	15-20	20-25	25-30
0 - .5	1.16	0.61	0.74	0.55	0.54	0.54
.5-1	0.82	0.53	0.59	0.47	0.53	0.52
1 -1.5	0.70	0.52	0.58	0.53	0.48	0.47
1.5-2	0.66	0.64	0.53	0.52	0.60	0.51
2 -2.5	0.68	0.61	0.62	0.51	0.63	0.61
2.5-3	0.58	0.58	0.53	0.56	0.59	0.53
3 -3.5	0.75	0.59	0.58	0.59	0.43	0.56
3.5-4	0.71	0.63	0.65	0.61	0.58	0.55
4 -4.5	0.59	0.50	0.59	0.60	0.53	0.51
4.5-5	0.55	0.55	0.51	0.59	0.65	0.57
Means for 5 min. period	0.72	0.58	0.59	0.55	0.56	0.54

data are summarized in table II. The differences between the means of the first 30 sec. period and the subsequent half minute periods during the first five minutes of recording were found to be statistically significant, with a probability of chance occurrence of $p<.001$. Because of this difference, the means of the first 5 min. of recording were significantly different from those of the second ($p<.001$), third ($p<.005$), fourth ($p<.001$), fifth ($p<.001$), and sixth ($p<.005$) 5 min. periods during the 30 min. experiment. The mean differences between the second, third, fourth, fifth, and sixth 5 min. periods were not significant, and in several cases no differences existed. Thus the mean responses showed no significant variance after the first 30 sec. of the entire 30 min. period.

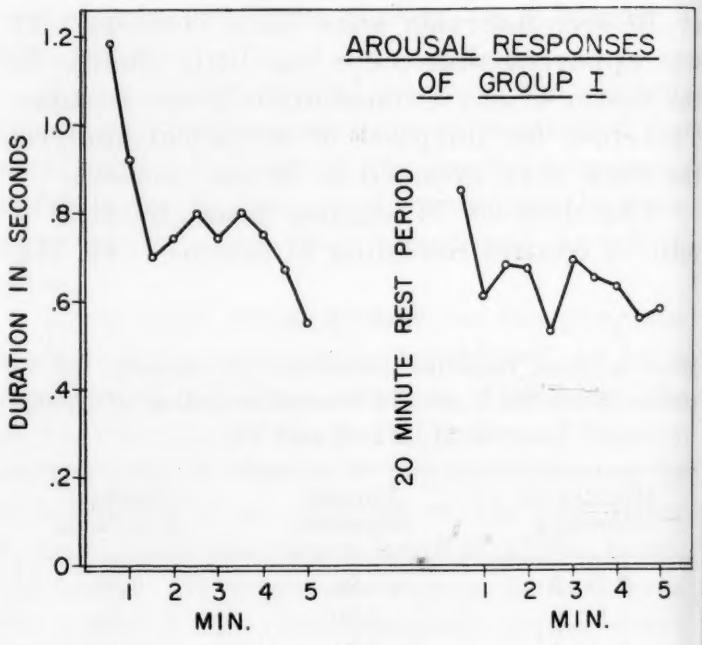

Fig. 3

TABLE III

Mean arousal response durations (in seconds), control and experimental periods.

Minutes of recording	Group I	Group II	Group III	Group IV	Group VI
0 - .5	1.18	1.18	1.16	1.39	1.37
.5-1	0.92	0.90	0.95	0.81	0.89
1 -1.5	0.70	0.79	0.72	0.78	0.64
1.5-2	0.74	0.78	0.66	0.71	0.62
2 -2.5	0.80	0.68	0.68	0.67	0.57
2.5-3	0.74	0.67	0.68	0.68	0.67
3 -3.5	0.80	0.76	0.58	0.61	0.69
3.5-4	0.75	0.62	0.67	0.51	0.69
4 -4.5	0.67	0.65	0.57	0.61	0.56
4.5-5	0.55	0.61	0.60	0.51	0.66
Means for 5 min. period	0.79	0.76	0.72	0.72	0.74
20 min. rest period					
0 - .5	0.85	0.75	0.79		0.95
.5-1	0.61	0.62	0.53		0.66
1 -1.5	0.68	0.64	0.48		0.65
1.5-2	0.67	0.58	0.58		0.63
2 -2.5	0.53	0.64	0.63		0.57
2.5-3	0.69	0.56	0.55		0.55
3 -3.5	0.65	0.74	0.54		0.63
3.5-4	0.63	0.65	0.48		0.61
4 -4.5	0.56	0.62	0.56		0.64
4.5-5	0.58	0.67	0.57		0.52
Means for 5 min. period	0.64	0.65	0.57		0.64

In group I the mean duration of the responses in the control period is significantly longer than the experimental period ($p<.05$). However, inspection of the data (fig. 3, table III) for the two periods demonstrates that the initial responses in the experimental period approximate but are not as great as the initial responses in the control period. After the first 30 sec. of the two periods, the mean response durations in the two groups were quite similar.

A brief lapse into sound sleep during the rest periods had no discernable effect on the arousal response duration of the involved subjects in the subsequent experimental periods, provided that they were called before stimulation was resumed. A further comparison of control periods obtained in two separate experiments done on different days (table IV) revealed no significant differences ($p>.20$) in the mean arousal response durations of 11 subjects, which were .78 and .71 sec. respectively.

TABLE IV

Comparison of mean arousal responses (in seconds) of 11 subjects on two different days.

Minutes of recording	Arousal Responses	
	Day 1	Day 2
0 - .5	1.16	1.03
.5-1	0.83	0.83
1 -1.5	0.72	0.68
1.5-2	0.77	0.62
2 -2.5	0.73	0.61
2.5-3	0.79	0.66
3 -3.5	0.78	0.69
3.5-4	0.70	0.71
4 -4.5	0.67	0.61
4.5-5	0.61	0.64
Means for 5 min. period	0.78	0.71

The effects of extraneous sound stimuli, such as the conversation common to most laboratories, were studied in groups II, III, and IV (table III). When the auditory stimulus was presented with the photic stimuli from the beginning of the experiment, with no prior control or rest periods (group IV), the mean arousal response durations were not significantly different from the control period of group I ($p>.40$). In group II, the auditory stimulus was presented during both the rest and the experimental periods, yet the latter was not significantly different from the experimental period of group I ($p>.50$). Similarly, omission of the auditory stimulus from the rest period resulted in no significant difference between the experimental means of group I and III ($p>.05$).

Study of the effects of attention on the arousal response duration showed no significant difference between the experimental periods of groups I and VI ($p>.20$), as seen in table III.

DISCUSSION

The findings in this investigation indicate that arousal responses elicited in the waking state by single photic stimuli are quite consistent. Although there is considerable individual variation in the duration of the response, the response is quite stable when the data of a group of subjects are considered.

Inspection of the first part of the mean response duration curve corroborates the work of Loomis *et al.* (1936) who observed a diminution in the response duration with time. Darrow *et al.* (1957) have as well described the same phenomenon with the application of sound stimuli in the waking state. The above investigators, however, terminated the experiment after the application of only a few stimuli. The present experiments were designed to determine the effects of prolonged administration of stimuli. It is clear that with repeated administration of photic stimuli at intervals averaging 10 sec. for 30 min., little diminution of the response duration occurs after the initial drop.

Glotfelty and Wilson (1956, 1958) compared arousal responses before and after the intravenous administration of tranquillizing drugs, using a 20 min. rest period between the control and experimental periods. The present experiments indicate that any significant differences in the arousal responses in such an experimental design are valid, as long as the initial half minute of each part of the exper-

iment are omitted from comparison. This comparison is possible because the significant difference between the control period and the experimental period lies entirely in the first 30 sec. of each. Twenty minutes of rest, even with sleep, does not allow complete recovery of the early arousal responses to control levels, but it has been shown here that recovery is complete after 24 or more hours have elapsed.

Extraneous stimuli which might arise in the laboratory apparently influence the arousal responses to an insignificant degree. The presentation of continuous sound stimuli during various phases of the experiment produces neither augmentation nor diminution of the response. Further, lack of influence on the arousal responses by the anecdotal stimuli indicates that changes in the levels of attention and of effect do not alter the responses. Since earlier workers demonstrated a diminution in the latency of the response when the subject had been instructed to follow the stimulus as quickly as possible with bulb squeezing (Loomis *et al.* 1938), it was deemed worthwhile to observe the effect of this technique on the response duration. No response duration effect is achieved by this motivational device, however.

The mediation of the arousal response by the reticular system has been demonstrated by many investigators, and is generally accepted. However, the arousal responses may reflect the ability of the cortex to react to changes in sub-cortical activity. Thus changes in arousal responses may not necessarily be assumed to represent an influence solely on subcortical neurones, but to indicate involvement of the arousal mechanism as a whole. Nevertheless, the normal data accumulated here makes possible the determination of the effects of drugs and disease on the arousal mechanism in the intact human.

SUMMARY

Observations on the duration of arousal responses elicited by single stroboscopic light flashes of constant intensity and duration have been made in 80 normal adults.

Normal values have been established for the response duration curves for periods up to 30 min.

The response duration in the first 30 sec. tends to be almost two times as long as the duration seen after 30 sec. The values then stabilize and remain stable for periods as long as 30 min. Recovery of the prolonged duration of the early responses is incomplete in 20 min. but complete after 24 hours.

Extraneous sound stimuli and attention have no effect on the duration of the arousal response.

The validity of using arousal response duration in assessing the influence of drugs and disease on central nervous system activity is established.

RÉSUMÉ

Chez 80 adultes normaux des observations de la durée de la réaction d'arrêt provoquée par des signaux lumineux stroboscopiques isolés d'intensité et de durée constante ont été faites. Les valeurs normales des durées de la réponse ont été établies pour des périodes allant jusqu'à 30 min. et ont été représentées graphiquement.

La durée de la réponse pendant les 30 premières secondes a une tendance à être deux fois plus longue que la réponse qu'on obtient après 30 sec. A ce moment les valeurs se stabilisent et restent constantes pour des périodes aussi longues que 30 min. Le rétablissement de la durée prolongée de la réponse précoce est incomplet après 20 min., mais est complet après 24 heures.

L'attention et des stimulis auditifs extérieurs n'influencent pas la durée de la réaction d'arrêt.

La valeur de l'usage de la durée de la réaction d'arrêt pour l'appréciation de l'influence de produits chimiques et de processus pathologiques sur l'activité du système nerveux central a été établie.

ZUSAMMENFASSUNG

Bei 80 normalen Erwachsenen wurde die Dauer der Weckreaktion im EEG, wie sie durch einen einzelnen stroboskopischen Lichtblitz von konstanter Intensität und Dauer ausgelöst wird, beobachtet. Normalwerte der Dauer der Reizantworten wurden kurvenmässig dargestellt während Beobachtungszeiten von bis zu 30 Minuten Dauer. Die Dauer der

Reizantworten in den ersten 30 Sekunden tendiert beinahe zwei mal so lang zu sein als diejenige, welche nach 30 Sekunden beobachtet wird. Die Werte stabilisieren sich dann und bleiben stationär für eine Periode bis zu einer Dauer von 30 Minuten. Wiederherstellung der langanhaltenden Reizantwort, wie sie im Frühstadium erscheint, ist nach 20 Minuten, noch unvollständig aber vollständig nach 24 Stunden. Exogene akustische Reize und erhöhte Aufmerksamkeit beeinflussen die Dauer der Weckreaktion nicht.

Es wird gezeigt, dass es berechtigt ist, die Dauer der Weckreaktion zu verwenden, um den Einfluss von Medikamenten und Krankheitsprozessen auf das Zentralnervensystem zu beurteilen.

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SEIZURE DISCHARGES EFFECTED BY INTRAVENOUSLY ADMINISTERED CONVULSANT DRUGS [1]

EEG and DC Changes in Cerebrum and Cerebellum of the Rabbit

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(Received for publication: May 12, 1958)

It was our purpose to compare the effects of a group of CNS stimulants upon the electrical activity of cerebral and cerebellar cortex. All agents used occasioned seizure discharge when injected intravenously. They were caffeine sodio-benzoate, picrotoxin, Metrazol, strychnine, thio-carbohydrazide, and dl-methionine-dl-sulfoxamine.

The use of calomel electrodes and D.C. recording permitted us to follow changes too slow to be detected by capacity-coupled amplifiers. Under the conditions of our experiments the immediate effect of an injection might be to unstabilize steady cortical potential (Goldring and O'Leary 1951a), resulting in random fluctuations of very slow time course and considerable magnitude. However, in the case of drugs having a long latent period such slow changes might appear shortly after injection and significantly precede the onset of seizure discharge. Because we could not correlate them directly with seizure periods we limited our attention to slow potential changes of shorter duration and lower amplitude which did provide firm correlations with the appearance and disappearance of convulsive activity.

METHOD

Of two pairs of calomel electrodes, one was arranged to record transcortically from the frontal granular cortex of the rabbit, the other between the surface of the cerebellar vermis and its depth. In both instances the surface-reference convention was followed. The potentials from two pairs of electrodes were led to the two channels of a D.C. amplifier and recorded upon a twin-beam cathode ray tube. Recording was done upon the x axis of the tube using continuous film advancement at a slow rate. A cystoscope light affixed to the tube's periphery provided a continuous track indicating the arbitrary baseline set for the experiment.

The rabbits (weight = 1.5 - 2 kg.) were prepared under ether. This included threading a polyethylene catheter through a femoral vein into the vena cava. Thereafter the animal was allowed to blow off the ether and for the remainder of the experiment Flaxedil (gallamine triethyl-iodide, 3 mg/kg.) and artificial respiration were substituted. Not more than one of the agents was tested per experiment and for each one used the experiment was repeated often enough to permit separating the less specific effect of some agents in unstabilizing SP from the more specific slow potential changes which occurred in relation to epochs of seizure discharge.

RESULTS

In the subsequent account changes of either cerebellar or cerebral cortical potential too slow to be followed accurately by a capacity-coupled amplifier will be referred to as shifts. Patterns such as ordinarily associated

[1] Aided by grants from the Institute of Neurological Diseases and Blindness, U.S. Public Health Service (B 1517), the Allen P. and Josephine B. Green Foundation, and the National Institute for Infantile Paralysis, CTAE.

with convulsion when recorded by a capacity-coupled amplifier will be referred to as seizure discharge. ECG will designate the usual spontaneous cerebral or cerebellar activity.

1. *Caffeine sodio-benzoate.* After a control period of observation, during which none of the changes to be described had appeared, after injection, cerebellar SP first shifting positively to usher in a tonic cerebellar discharge of 30/sec. frequency and 150 μV. amplitude. This endured 2-5 sec. (fig. 1 B 2) during which time there was no change in ECG although cerebral SP did commence to shift positively (fig. 1 B 1 compared with

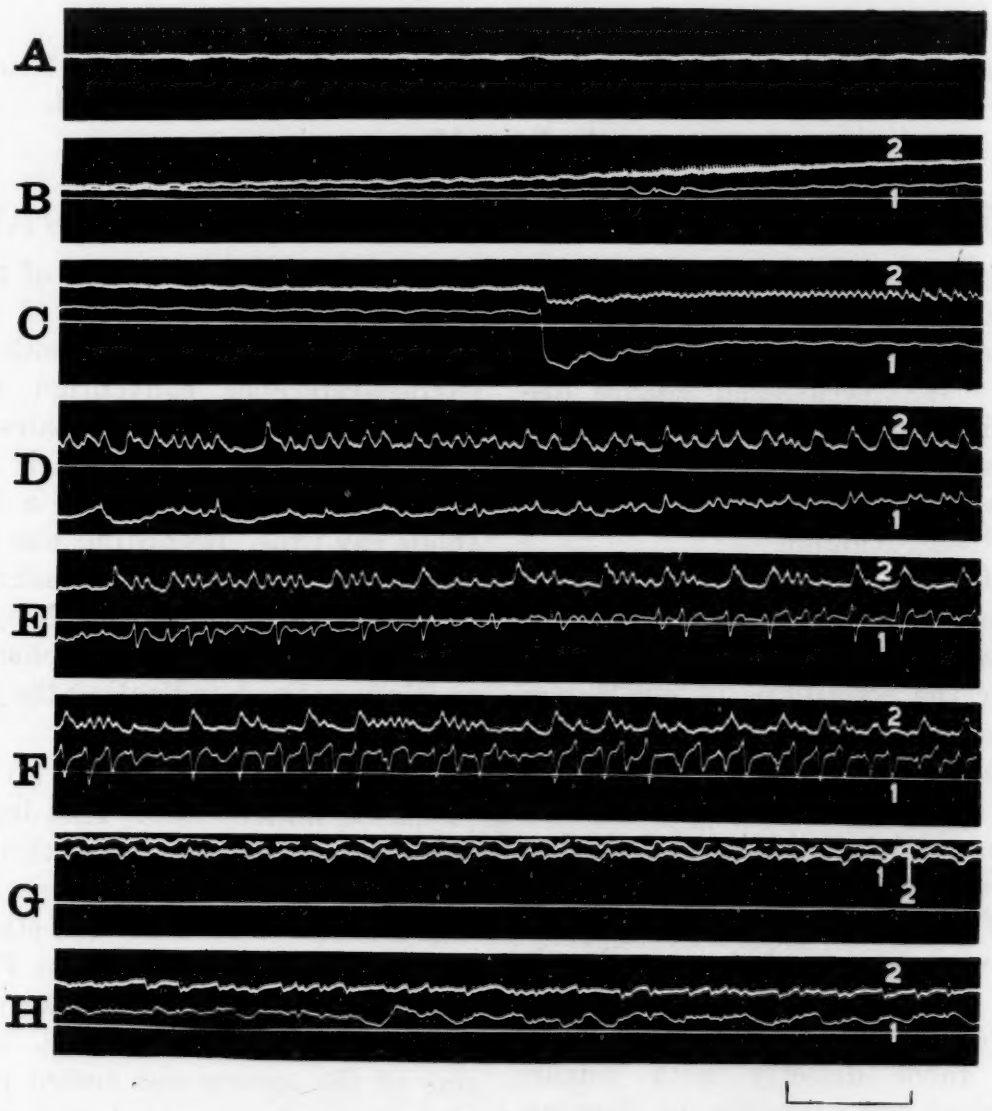

Fig. 1

Changes accompanying caffeine induced seizure discharge. A, resting record prior to drug injection. Note that both cerebral and cerebellar trace hug baseline. B, 10 sec. after the injection of 450 mg. of caffeine. Strip B - F, continuous; F - G, 1 min. interval; G - H, 3 min. interval. The following features are alike for all figures: Cerebral trace labelled 1; cerebellar trace 2; baseline, straight unlabelled. Parameters righ lower corner: Horizontal, 1 sec.; longer and shorter vertical lines indicate cerebellar and cerebral sensitivities, respectively 500 μV. cal. signal.

250-450 mg. caffeine was injected in 15 sec. This quickly activated a seizure discharge in both cerebrum and cerebellum. A single injection produced only one epoch of discharge, although after the first intense seizure burst the activity could wax and wane for as long as 5 min. The initial change appeared 5 sec. 1 A). Tonic activity then disappeared from the cerebellar trace. About 8 sec. later a precipitous negative shift appeared in both traces, larger in the case of the cerebral one (fig. 1 C, middle) which crossed the baseline into negative territory. Overt seizure activity developed with the appearance of this shift, oc-

curring at both cerebral and cerebellar leads but with slower build-up at the cerebral combination (fig. 1 C 1 and D 1). As the cerebral seizure discharge increased in voltage the SP shifted back toward its original level, recrossing the baseline into positive territory (fig. 1 E, middle and 1 F). Cerebellar SP also shifted more positively as seizure activity developed, although the reaction in that trace was not so decided since the preceding negative shift had been less intense. After these changes the SP of both traces returned to the baseline to remain there until another injection was made.

2. *Picrotoxin.* Ordinarily a 6 mg. injection produced a characteristic sequence of changes in cerebrum and cerebellum. The change developed slowly at both sites and was always much less evident in the cerebellum. Figure 2, taken from a single experiment, illustrates the sequence of events which took place. Two to 5 min. after injection both cerebral and cerebellar SP commenced to shift negatively (fig. 2 B). Then a suddenly developing negative cerebral shift (fig. 2 C, left) ushered in a sequence of slow waves (fig. 2 C and D, 1) seen only in that trace. After 5-10 min. (15 min. from the injection) these

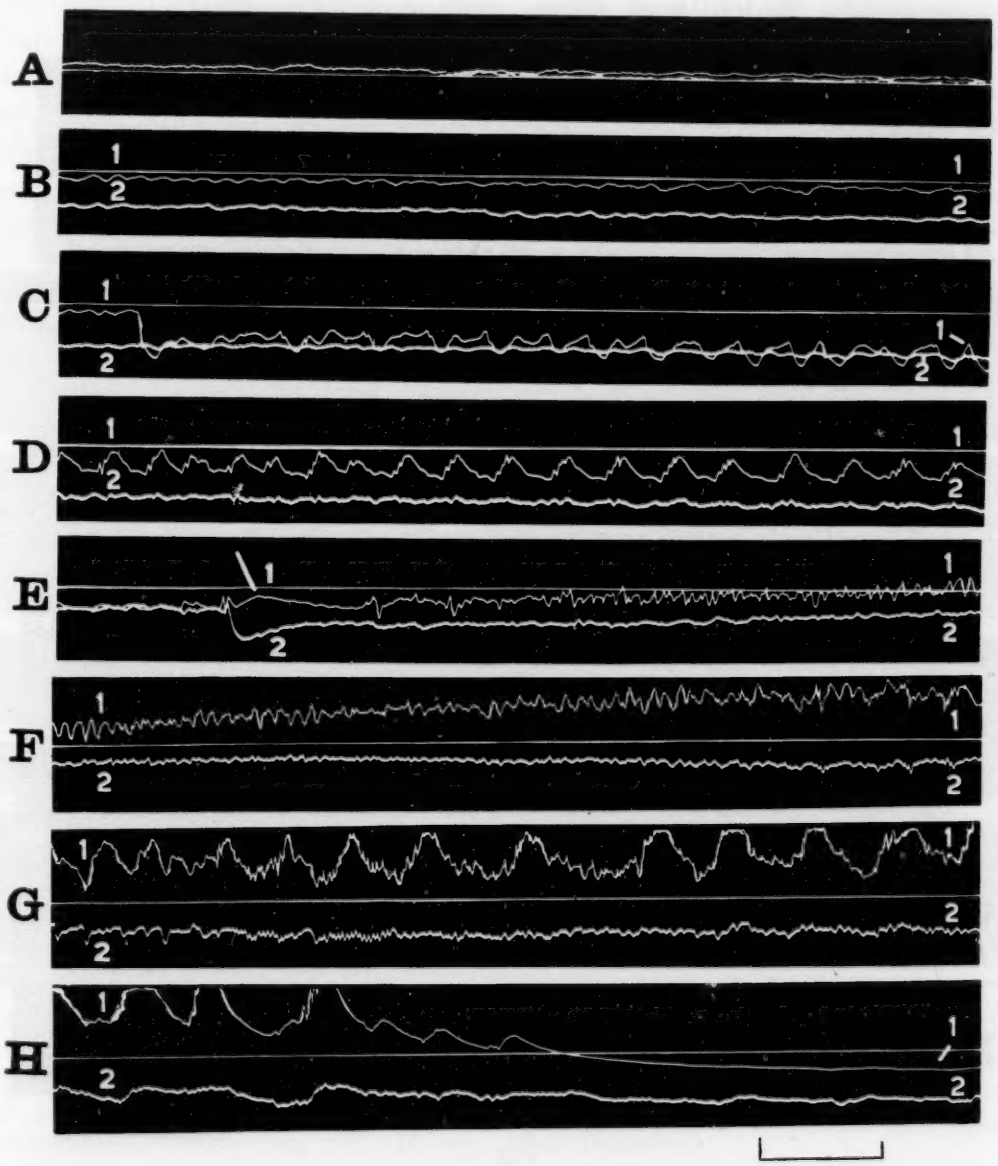

Fig. 2

Changes accompanying picrotoxin induced seizure discharge. Cerebral, 1; cerebellar 2. A, resting SP prior to injection; B - H, continuous strips following 6 mg., picrotoxin. Time intervals between A - B, C - D, and D - E are 4-½ min., 3-½ min., and 10 min. respectively. Strips E - G are continuous and there is a 10 sec. interval between G - H. Changes are described in the text which relate to omitted portions of record.

slow waves disappeared. The cerebellar SP then returned partially toward the baseline, cerebral SP not changing further (fig. 2 E, left). At this point cerebellar SP suddenly shifted negatively, a minimal positive shift developing simultaneously in the cerebral trace (fig. 2 E, arrow). These shifts ushered in fast seizure discharge which was more slow waves and disappearing (fig. 2 G and H). As the slow waves were lost, and the trace became isoelectric for usual ECG activity, SP underwent a marked negative shift (fig. 2 H). Near the end of cerebral paroxysm cerebellar discharge also disappeared, SP in that trace showing a less impressive slowly developing minor negative shift.

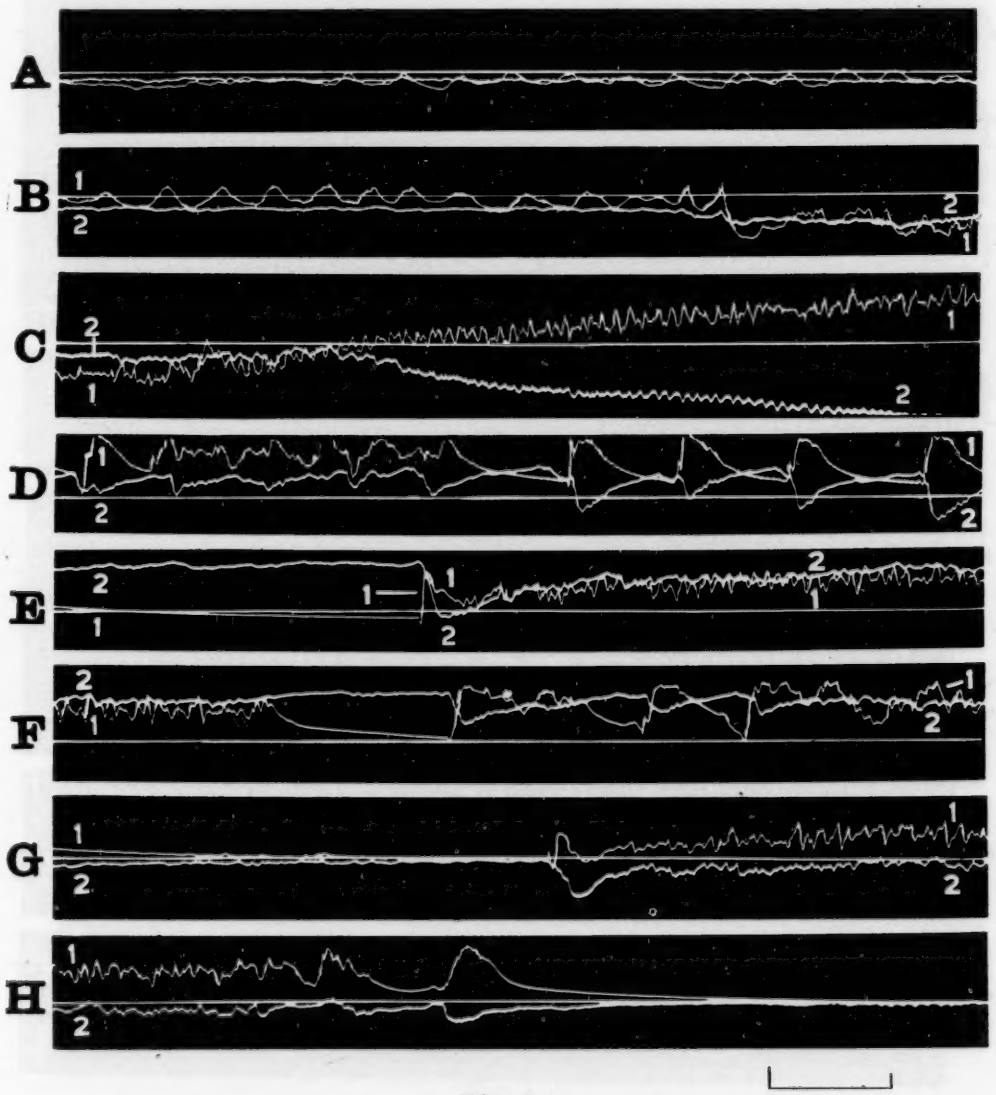

Fig. 3

Changes with seizure discharge induced by the i.v. injection of Metrazol. A, resting SP prior to injection. B - H, representative strips taken from continuous tracing following 150 mg. Metrazol. Time interval between A and B, 6 sec. B - C, E - F, G - H are continuous records. Intervals between C - D, D - E and F - G are 45 sec., 4 min. and 8-½ min. respectively. The text provides a description of portions of the trace omitted.

evident in the cerebral combination. As the fast discharge built up the cerebral SP shifted positively (fig. 2 E 1 and F 1); by contrast, a transient minor positive cerebellar shift developed as low amplitude seizure discharge appeared at that lead. Seizure discharge continued in the cerebral lead, ultimately breaking up with the appearance of large amplitude

Such sequences occurred over and over following a single picrotoxin injection, each such sequence being characterized by the same SP shifts. In occasional animals the cerebral discharge would continue upon a negatively shifted baseline, breaking up to terminate only as SP regained positivity to return toward the pre-injection baseline.

3. *Metrazol.* Five to 10 sec. after the injection of 100 - 200 mg., a negative cerebral SP shift developed suddenly (fig. 3 B) followed by seizure activity at that lead. There were no concurrent alterations in the cerebellar trace. However, as the paroxysm continued diverging SP shifts became evident, the cerebral trace shifting positively and that of the cerebellum negatively (fig. 3 C). Then seizure activity, hitherto absent in the cerebellar trace, appeared upon the negative shift (fig. 3 C 2). For the remainder of a Metrazol-induced seizure the changes were not identical for all experiments. However, traces D - H of this experiment do indicate the commoner late occurrences. That of D, taken 45 sec. after C, found seizure activity in progress upon a positive shift in both cerebral and cerebellar leads. During strip D that seizure pattern was replaced by recurring sharp front slow waves of 0.5 sec. duration. These appeared in mirror image in the two leads, cerebral positive and cerebellar negative. Between strips D and E several such bursts intervened, after each one cerebral SP shifting negatively and cerebellar positively. In figure 3 E *left* the quiet interval was a prelude to the appearance of a new pattern of seizure discharge. The latter arose out of a sharply developing mirror image shift of SP at the two leads, cerebral positive and cerebellar negative (fig. 3 E, middle). At the cerebral lead the seizure pattern developed immediately after the positive SP shift. At the cerebellar one the trace regained its pre-shift status (fig. 3 E, right) without the appearance of paroxysmal sequences. Such a pattern usually terminated in a rapidly developing cerebral/negative, cerebral/positive shift (fig. 3 F, left).

Similar relations between seizure activity and SP shift recurred for the remainder of a usual experiment (20 - 30 min.). For example, in figure 3 F, *right* note three shorter duration replicas of the change just described for figure 3 E and 3 F, *left*. In figure 3 G and H, tracings obtained 8 min. after the end of F, there is a similar pattern of seizure activity.

4. *Strychnine.* The changes varied with the size of the injection. Small amounts (500 μg.) altered the cerebellar trace alone, whereas larger doses produced seizure activity and changed the SP at both cerebral and cerebellar leads. After 5 - 10 sec. a 500 μg. injection caused a striking change in the cere-

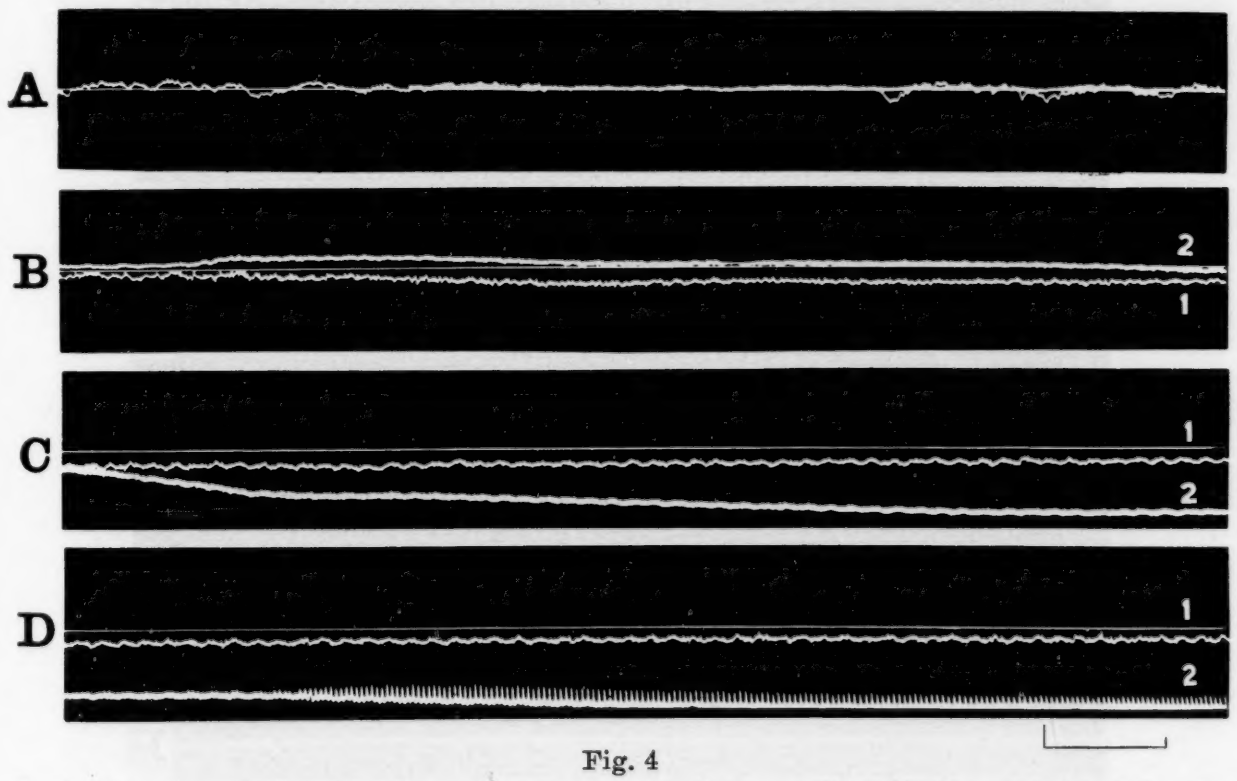

Fig. 4

Cerebral and cerebellar SP changes accompanying the cerebellar discharge induced by i.v. injection of strychnine. A, resting SP prior to drug injection. Note that both cerebral and cerebellar traces hug the baseline. B - D continuous strip following the injection of 500 μg. strychnine, commencing (B) 16 sec. after injection.

bellar trace (fig. 4 B, C and D), a minor positive SP shift preceding a rapidly developing 1 - 2 mV. negative one (fig. 4 C). Concurrently with the latter (fig. 4 B and C) the thickness of the cerebellar line increased due to the development of low amplitude fast discharge. Ten sec. after the start of the negative trace either showed no change or at most underwent a minor negative shift (fig. 4 B, C and D). If no additional strychnine was injected the cerebellar SP remained shifted negatively for at least 3 min., the rhythmic discharge meanwhile waxing and waning. With the cessation of the latter cerebellar SP

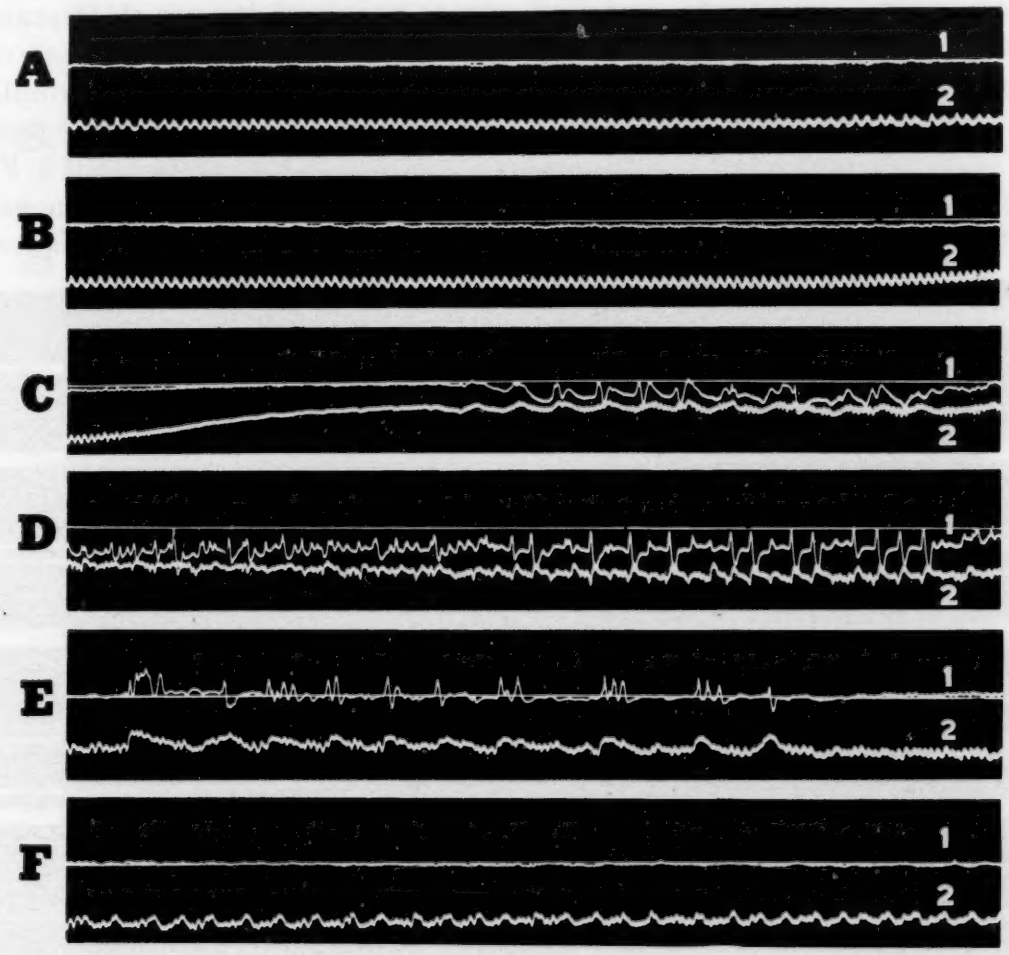

Fig. 5

Cerebral (line 1) and cerebellar (line 2) SP change accompanying seizure discharge activated by i.v. strychnine, 3.0 mg. Injection was made during strychnine-induced rhythmic cerebellar discharge. Strip A (2) pre-injection, shows rhythmic cerebellar discharge in progress upon a negatively shifted baseline; cerebral trace (1) unaltered. Interval between A and B, 5 sec.; B and C are continuous records. Intervals of 12 and 9 sec. occur between C and D, and D and E respectively. There was no interval between E and F. Detailed description is provided in the text.

cerebellar shift a 30-50/sec. 200 - 300 μV. discharge of comb-like appearance (fig. 4 D) developed. Uniformity of rate and amplitude distinguished it from the usual seizure activity noted in cerebrum or cerebellum of these experiments. This pattern was seen earlier by Markham, Browne, Johnson and Walker (1951) and called "rhythmic" discharge; hereafter we will use their term for it. During this sequence of cerebellar events the cerebral might either remain shifted negatively or return slowly to its pre-injection baseline.

If a larger amount (1.5 to 3.0 mg.) of strychnine was injected during the rhythmic discharge, other findings developed as illustrated in figure 5 from another experiment. Figure 5 A 2 shows cerebellar SP shifted negatively and rhythmic discharge in progress as illustrated in figure 4. Four sec. after the injection of an additional 3 mg. of strychnine

a rapidly developing positive cerebellar shift was observed and simultaneously the previously evident rhythmic discharge disappeared. As the cerebellar shift levelled off the cerebral trace shifted negatively, seizure discharge appearing there as well (fig. 5 C, right). Somewhat later a seizure of similar pattern arose from the cerebellum (fig. 5 D). This cerebellar discharge continued, waxing and waning in voltage, for the 45 min. remaining in the experiment, the negative cerebellar shift also persisting (fig. 5 D, E and F). The cerebral seizure activity differed from that of the cerebellum in occurring in runs of 10 - 15 sec., SP shifting positively as a run continued (fig. 5 D, E and F) and undergoing a reverse negative shift (or none) as the run terminated. This pattern of seizure activity and associated shift recurred again and again during the remainder of the experiment.

5. *Thiocarbohydrazide* (*thio-c.*). The changes following thio-c. (40 mg.) developed slowly starting 20 - 40 min. after injection. Two patterns of response were noted. The first, usually seen early, is shown in figure 6. Strip A, 20 min. after the usual injection showed cerebral SP (1) commencing to shift negatively, cerebellar SP (2) meanwhile showing no change. As the cerebral SP shift continued seizure activity developed there, the cerebellar trace still remaining unaffected (fig. 6 B, C, D and E). With subsidence and final disappearance of cerebral seizure, the SP there lost negativity, shifting back to the baseline (fig. 6 F, G and H). In this instance a cerebral SP change and seizure occurred

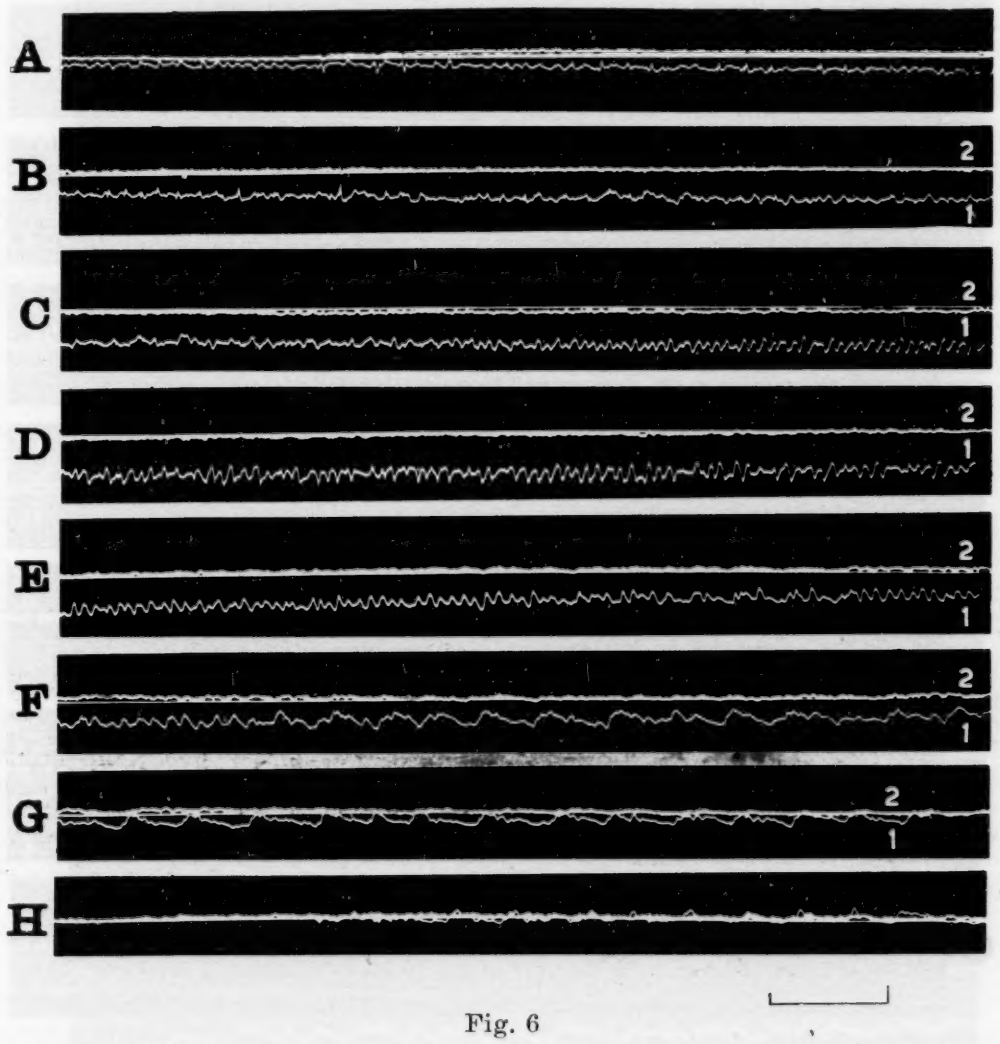

Fig. 6

Seizure discharge induced by the i.v. injection of thiocarbohydrazide. A, 20 min. following 40 mg. Strips A - D are continuous as are G - H. Time intervals between D - E, E - F, and F - G are 4 sec., 18 sec. and 8 sec., respectively. Portions of record omitted showed no significant changes. The cerebellar trace is not readily discerned in the majority of strips since it straddles the baseline closely.

without a corresponding change in cerebellar ECG or SP.

At longer intervals after an injection patterns of seizure discharge and associated SP change developed which were similar to those seen with picrotoxin and Metrazol. Fig. 7 shows tracings from two different experiments to illustrate these changes. Figure 7 A and B were obtained 1 hour after a 30 mg. developed at the start of cerebral seizure discharge. As the voltage of the cerebral paroxysm increased its SP shifted positively across the baseline (fig. 7 C and D, 1). Meanwhile (fig. 7 B right and C) the cerebellar trace recovered rapidly from the transient negative shift it had undergone previously, and seizure activity became evident there too (fig. 7 C right and D 2). At the terminus

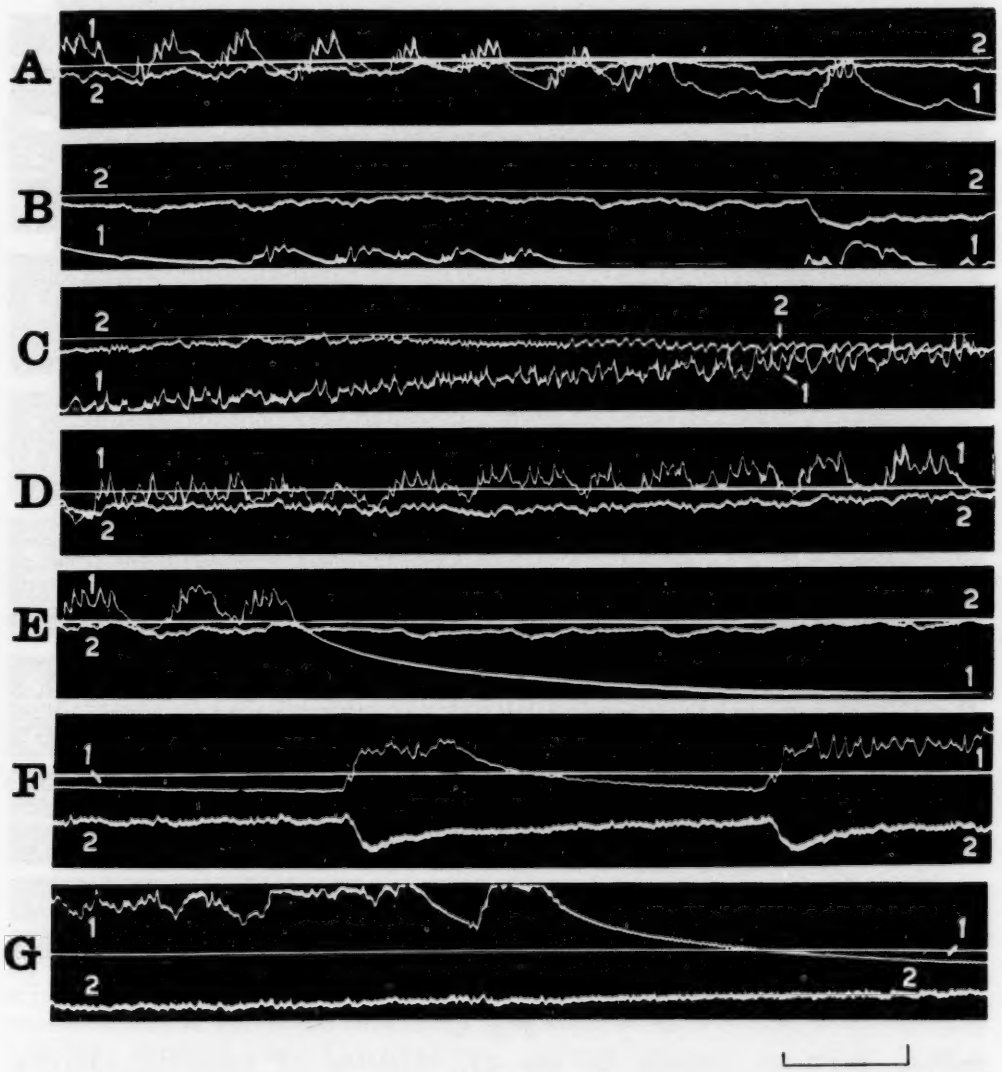

Fig. 7

Other changes which accompany seizure discharge induced by i.v. injection of thiocarbohydrazide. Tracings in A - E are continuous and were obtained 1 hour following injection of 30 mg. Tracings F - G were obtained from another animal 1-½ hours following 80 mg. Detailed description in the text.

injection. They show a negative cerebral shift occurring as the seizure breaks up (fig. 7 A, right) to disappear (fig. 7 B, left). Cerebellar SP underwent little change during this disappearance of cerebral paroxysm. In strip B, *middle,* the cerebral seizure activity reappeared; shortly thereafter a suddenly developing negative cerebellar shift occurred fig. 7 B, right 2). More commonly the latter of the cerebral seizure SP shifted negatively there without a similar occurrence in the cerebellum (fig. 7 E). Figure 7 F and G, traces from another experiment, show an analogous change illustrating the marked similarity between late thio-c. changes and those of Metrazol (fig. 3 G and H) and picrotoxin (fig. 2 E - H).

Another of the occurrences with thio-c. was

a marked amplitude reduction of cerebral ECG association with a negative shift resembling that of spreading depression (Leão 1947).

6. *Dl-methionine-dl-sulfoxamine.* This agent was isolated following evidence that seizures could be due to the ingestion of nitrogen trichloride-treated flour (Fortmann, Parker and Reiner 1951). The change, which followed the injection of 0.7 to 1.0 g. of the active agent, developed slowly, requiring 1 to 2 hours for its maturation. It was limited to the cerebrum, only minor inconstant changes of questionable significance occurring at the cerebellar lead. The earliest cerebral change noted was a negative/positive shift with no related seizure discharge. Such a shift might develop as late as 2 hours after injection, nothing of note occurring in the interim. The negative phase of the shift could reach a crest of 3 - 10 mV. in 20 - 30 sec.; as it did so, fast activity of low voltage appeared (fig. 8 A, B, C, D and H). In the succeeding 15 sec. the negativity receded and the trace continued across the baseline into positive territory, the fast activity disappearing (fig. 8 E and F). After being shifted positively for 1 to 2 min. SP then returned to the baseline. Such swings

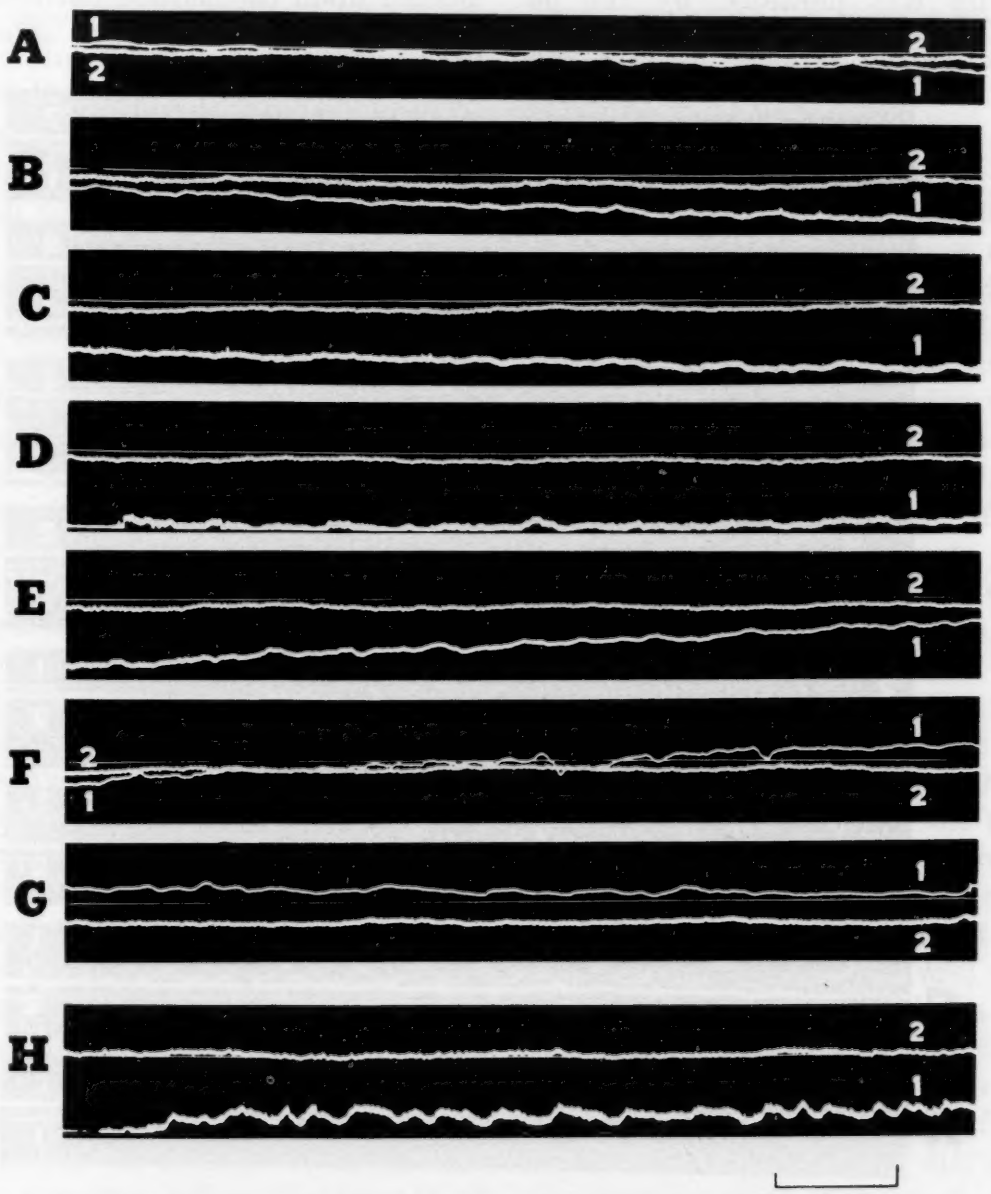

Fig. 8

Changes following the injection of dl-methionine-dl-sulfoxamine. A, 1 hr. following drug injection. A - C, continuous; C - D, 4 sec. interval; D - F, continuous; F - G, 33 sec. interval. H, record obtained from another animal during negative shift. Note the low voltage fast activity in the cerebral trace.

would occur repeatedly for an hour or more. After one or more cycles, seizure activity appeared in the trace as SP recovered from the negative shift and commenced its positive excursion (fig. 9). With succeeding repetitions the seizure discharge appeared earlier during the recovery from the negative shift. Its appearance usually was heralded by the occurrence of 1 - 2 mV. slow waves (fig. 9, E and F). After its appearance the seizure activity continued for 30 - 120 sec., disappearing as SP returned to the baseline from the second or positive phase (fig. 9 G and H). In some animals with several recurrences of the seizure cycle low voltage seizure activity occurred during the negative shift, disappearing before the crest of the negative phase had been reached. With this exception the events of the succeeding cycles were similar to the earlier ones.

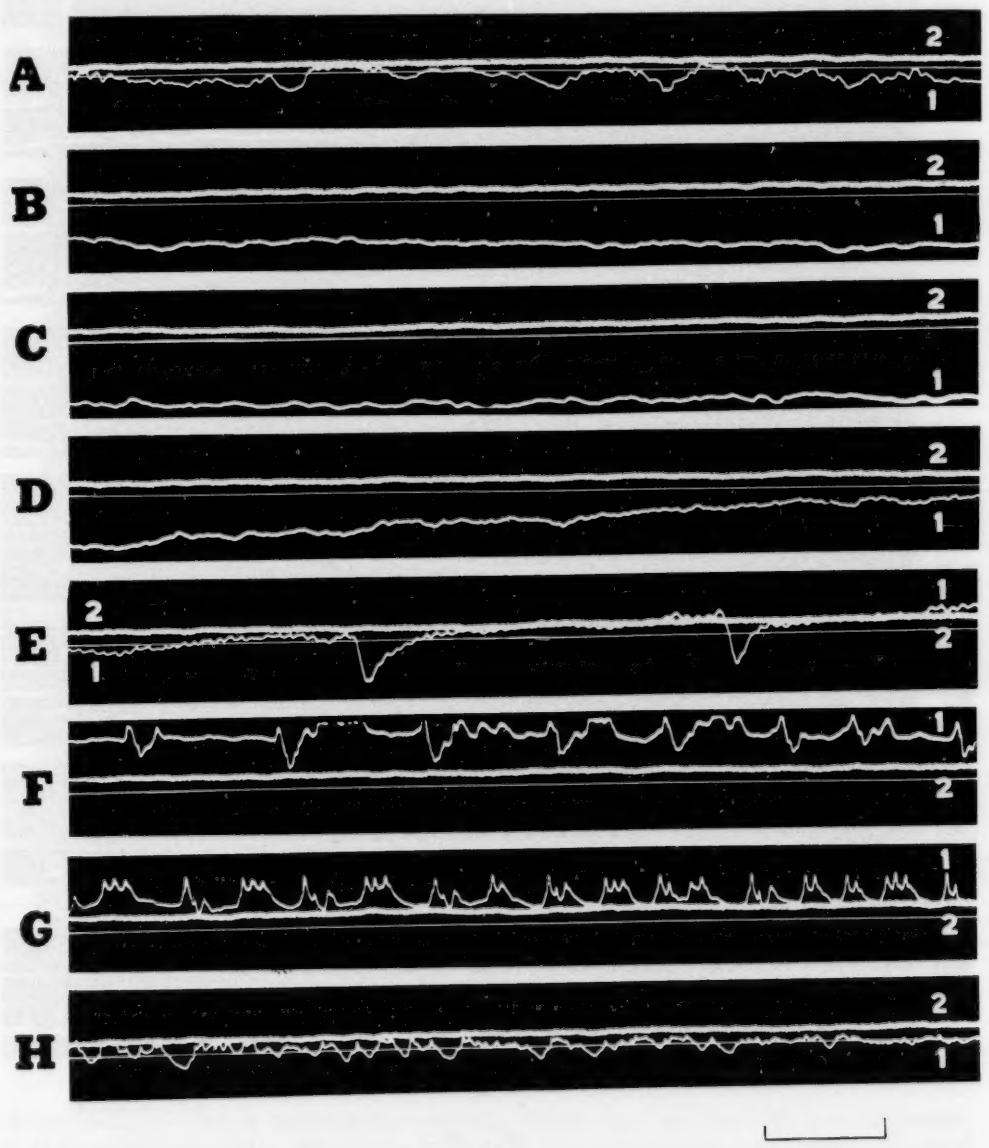

Fig. 9

Changes with seizure discharge induced by i.v. injection of dl-methionine-dl-sulfoxamine. A, 2 hr., 45 min. after i.v. injection of drug. A - B, B - C, C - D, D - E, E - F, F - G, G - H are 5 sec., 7 sec., 9 sec., 1 sec., 1 min., 8 sec., and 26 sec. intervals respectively.

DISCUSSION

Several groups of investigators have reported upon the seizure patterns of cerebrum and cerebellum that occur subsequent to the intravenous injection of different activating agents. Fischer and Löwenbach (1934, I and II) described the convulsoid patterns seen in rabbit visual cortex subsequent to the injection of strychnine, Metrazol, picrotoxin and caffeine; and Pfeiffer, Jenny and Marshall (1956) reported corresponding patterns for

thio-c. and related hydrazides in monkey and man. Studies upon cerebellar alterations have been carried out by Markham, Browne, Johnson and Walker (1951, strychnine, Metrazol, picrotoxin and caffeine), Marossero and Garrone (1952, Metrazol and strychnine) and Swank and Brendler (1951, picrotoxin), and of combined cerebellar and cerebral alterations by Goodwin, Kerr and Lawson (1940, Metrazol), and Purpura and Grundfest (1957, strychnine and Metrazol). In brief, the agents differed in the thresholds of cerebellar as compared with cerebral seizure discharge, in time of onset after injection, in form of the discharge (for example rhythmic cerebellar discharge), and in simultaneity of spiking activity at the two sites. To these the present study adds the SP changes that occur.

Our past work has established three origins for such slow potential phenomena of the cortex as are under investigation here. There could also be unidentified ones. (1) Singly or serially evoked responses, including usual specific responses of sensory cortex (Goldring and O'Leary 1951), dendritic (Goldring, O'Leary and Huang 1958) and recruiting transients (Goldring and O'Leary 1957) can have both positive and negative after-effects which sum variously but predictably in the response to serial stimulation at different frequencies. (2) In the instance of dendritic and recruiting waves, a succession of responses which derive from graded response elements (i.e., dendrites), the transients themselves become incorporated into the slow potential shift occasioned by high frequency stimulation, due presumably to failure of the dendrite membrane to recover from the response to one stimulus before the impact of the next one (Clare and Bishop 1955). (3) Veratrine applied to the cortical surface results in cyclic negative shifts, each of 5 min. duration and amounting to 5-15 mV. (Goldring and O'Leary 1954). With each such negative plunge the components of the evoked visual response are lost successively in an order suggesting the downward spread of a wave of depolarization initiated at the cortical surface: with recession of the wave toward the surface the evoked response components are regained in reverse order. Such a D.C. shift is evidently akin to that which occurs as a spreading wave in Leão's depression (Leão 1947). It is perhaps also analogous to the abrupt negative cerebral shift which initiated seizure discharge with Metrazol and similar cyclic shifts with dl-methionine-dl-sulfoxamine, both as observed in these experiments. Thus explained, a negative shift appearing abruptly in inactive cortex as a prelude to seizure takes on significance as a stage in seizure development readily missed by a capacity-coupled amplifier.

The preceding brief summary condenses much of our prior experience which can be of aid in interpreting the seizure activation phenomena described here. In other earlier work we have shown that cerebral cortical seizures can be initiated directly by surface-positive polarization (Goldring and O'Leary 1951) and indirectly by repetitive stimulation applied to a relay nucleus of the thalamus, such as the lateral geniculate nucleus for the visual cortex (Goldring and O'Leary 1951). In each of these instances (rodent) a positively directed slow potential shift develops along with the rise in amplitude of the seizure discharge, continues through the seizure, and is replaced by an opposite negative shift at its end and the beginning of the post-ictal quiescence. In rabbits cerebral SP can be made unstable by excesses of either type of stimulation, leading to frequent trains of spontaneously originating seizure discharge, each such train also being accompanied by a positive shift. We believe that the explanation for such a positive shift resides chiefly in the summation of the positive after-effects of the spike processes. It is much more difficult to explain the negative shift of the post-ictal period as a summation of negative after-effect since this shift significantly outlasts the end of seizure. Thus such individual after-effects as may be presumed to multiply as a result of intensive neuronal discharge during the seizure would need to be quite prolonged to give rise to such a post-ictal summation phenomenon. However, an analogy can be drawn between this post-ictal negativity and the increase in amplitude and prolongation of the summed negative after-effect of serially evoked dendritic responses as barbiturate anesthesia is progres-

sively deepened (Goldring, O'Leary and Huang 1958). In both situations the negativity may be inferred to indicate that neuronal depression has occasioned significant slowing of recovery (i.e. of repolarization). Thus to postulate summation of negative after-effect as the explanation for the post-ictal negative shift is not as far-fetched as we believed formerly.

This leads to the inquiry whether *all* negative shifts signify depression of cortical elements. This cannot be so in the case of those which precede intensive seizure discharge, as occasioned by thio-c. and methionine sulfoxamine in these experiments. Insofar as cortical seizure phenomena appear as an after-discharge to periods of intensive stimulation (such as occasions a negative cortical shift from intralaminar thalamic stimulation) the burst may begin and end upon a negative shift but only if it is of brief duration. Where a train of post-stimulatory discharge is prolonged SP shifts positively as the train grows in length even if it commenced from a negatively shifted base. Thus the distinction made earlier between post-stimulatory cortical seizure discharge developing from a negative SP shift in the case of intralaminar and from a positive one in that of thalamic relay nucleus activation is apt to prove artificial (Goldring and O'Leary 1957).

In the series of convulsive agents under comparison here it was only the early seizure relations between SP and ECG which proved specific. By contrast late changes were non-specific, marked similarities often occurring between seizure changes effected by different agents. Examples of early specifities were: the positive cerebellar SP shift preceding the appearance of tonic cerebellar discharge in the case of caffeine (fig. 1 B), the divergent SP shifts with Metrazol (cerebellar/negative; cerebrum/positive) which relate to the development of cerebellar seizure discharge (fig. 3 C), the negative cerebellar shift which introduces the rhythmic cerebellar discharge occasioned by strychnine (500 μg., fig. 4 C), and the positive cerebellar shift with disappearance of that discharge upon the injection of additional strychnine (1.5 - 3.0 mg., fig. 4 C). The cyclic negative cerebral shifts which develop after a long delay with methionine sulfoxamine (fig. 9), seizure activity usually recurring in increasing amount, amplitude and duration with the successive shifts, is another example of an individualized response to a convulsive agent. However, it may be analogous to the negative cerebral shift with caffeine (fig. 1 C), picrotoxin (fig. 2 C) and Metrazol (fig. 3 B). In all of these instances a negative cerebral shift develops explosively and is a prelude to the appearance of seizure discharge.

Non-specific effects appeared late in the experiments with picrotoxin, Metrazol and thio-c. The late patterns for all three drugs were very similar and consisted in suddenly developing mirror image shifts (cerebrum/positive; cerebellum/negative) followed by the appearance of seizure discharge, especially at the cerebral lead combination. As that seizure discharge continued, cerebral SP shifted still more positively, while the cerebellar lead (at which no seizure activity had appeared) only recovered from its preceding positive shift. At the end of a run of seizure discharge cerebral SP would again shift negatively, the cerebellar trace continuing unchanged (compare fig. 2 D - H, picrotoxin with fig. 3 G, H, Metrazol, and fig. 7 F - G, thio-c.).

SUMMARY

Employing transcortical recording and D.C. amplification, changes were recorded simultaneously in cerebrum and cerebellum incident to the intravenous injection of convulsant drugs. Caffeine, strychnine, picrotoxin, Metrazol, thio-carbohydrazide and dl-methionine-dl-sulfoxamine were the drugs investigated. Major SP changes might commence early following an injection and continue throughout. The significance of these was impossible to assess as they occurred before seizure discharge had developed, were of very slow time course and not intimately related to the appearance and disappearance of seizure discharge at any time.

For each drug we provide a description of the sequence of seizure discharge and of the

associated SP changes. Those SP changes which were agent specific ordinarily accompanied the early seizure trains of an experiment. Later several of the drugs (picrotoxin, Metrazol and thio-c.) produced nearly identical patterns. Dl-methionine-dl-sulfoxamine was unique for its long latent period and for the several negative/positive shifts which might precede the development of seizure trains. When they appeared seizure trains did so with respect to an identical shift and recurred in the same relation with each succeeding shift.

In some instances two drugs might produce the same pattern of seizure discharge but SP changes of opposite polarity. Then the SP shift distinguished the trace occasioned by one drug from that of the other.

RÉSUMÉ

Employant des enregistrements transcorticaux et utilisant des amplificateurs à courant direct les altérations produits par l'injection intraveineuse de drogues convulsivantes ont été enregistrées simultanément sur l'écorce cérébrale et le cervelet. Les effets de la caféine, de la strychnine, de la picrotoxine, du Cardiazol, du thio-carbohydrazide et de la dl-methionine-dl-sulfoxamine ont été ainsi étudiés. Il a été observé que des changements importants du potentiel lent peuvent commencer tôt après l'injection de la drogue et continuer pendant toute la période de celle-ci. La signification de ces altérations lentes est impossible à élucider vu leur développement avant l'apparition de la décharge convulsivante, leur évolution temporelle excessivement lente et vu l'absence d'une corrélation intime entre ces altérations lentes et l'apparition et la disparition de la décharge convulsivante.

Les auteurs décrivent la séquence des décharges convulsivantes et les altérations du potentiel lent associées avec celle-ci, tels qu'ils sont produit par chacune des drogues étudiées. Les altérations du potentiel lent qui étaient spécifiques pour un certain agent chimique accompagnaient en général les manifestations précoces d'une décharge convulsivante. Plus tard plusieurs des drogues (picrotoxine, Cardiazol et thio-carbohydrazide) produisaient des changements à peu près identiques. L'effet de la dl-methionine-dl-sulfoxamine était unique en ce que la période de latence était très longue et en ce que plusieurs déplacements négatifs et positifs du niveau du potentiel étaient susceptibles de précéder le développement d'une décharge convulsivante. Les séquences de décharges convulsivantes apparaissaient en relation avec des déplacements identiques de la ligne de base du potentiel lent et se reproduisaient avec chaque déplacement consécutif montrant la même relation avec celui-ci qu'auparavant.

Parfois deux médicaments produisaient le même type de décharge convulsivante mais des déplacements de la ligne de base du potentiel lent en directions opposées. Dans ce cas c'était le déplacement du potentiel lent qui permettait de différencier l'effet d'une drogue par rapport à celui produit par l'autre.

ZUSAMMENFASSUNG

Mit Hilfe von transkortikalen Ableitungen und Gleichstromverstärkern wurden Veränderungen, wie sie durch intravenöse Injektion von krampferzeugenden Medikamenten hervorgerufen werden, gleichzeitig im Gross- und Kleinhirn aufgezeichnet. Die Wirkung von Koffein, Strychnin, Pikrotoxin, Kardiazol, Thiocarbohydrazid und dl-Methionin-dl-Sulfoxamin wurde auf diese Weise untersucht. Deutliche Änderungen im Gleichstromniveau können früh nach der Injektion auftreten und während der ganzen Injektionsperiode andauern. Die Bedeutung dieser Veränderungen konnte nich abgeklärt werden, da sie schon auftraten, bevor eine epileptische Entladung sich entwickelte und einen sehr langsamen zeitlichen Ablauf aufwiesen. Auch waren diese Veränderungen niemals eng verknüpft mit dem Auftreten oder Verschwinden von Anfallsentladungen.

Für jedes Medikament wird eine Beschreibung der Abläufe der Anfallsentladung und der verassoziierten Gleichstromveränderungen gegeben. Diejenigen Gleichstromveränderungen, welche spezifisch waren für ein bestimmtes Medikament, ereigneten sich allgemeinen gleichzeitig mit der Frühphase einer Anfallsentladung. Später produzierten ver-

schiedene Medikamente (Pikrotoxin, Kardiazol und Thiocarbohydrazid) fast identische Veränderungen. dl-Methionin-dl-Sulfoxamin nahm eine Sonderstellung ein, da eine sehr lange Latenzperiode verstrich, bevor verschiedene negativ-positive Verschiebungen des Gleichstromniveaus auftraten, welche manchmal der Entwicklung von Anfallsentladungen vorausgingen. Wenn diese auftraten, so erschienen die Krampfpotentiale in Korrelation mit identischen Verschiebungen des Gleichstromniveaus und ihr wiederholtes Wiederauftreten zeigte stets dieselbe Beziehung mit jeder nachfolgenden Verschiebung des Gleichstromniveaus.

Manchmal wurde beobachtet, dass zwei Medikamente den gleichen Typ von Anfallsentladungen produzierten, dass jedoch die Gleichstromverschiebungen von gegensätzlicher Polarität waren. In diesen Fällen war es die Richtung der Gleichstromveränderung welche es ermöglichte die respektiven Kurvenbilder der beiden Medikamente voneinander zu differenzieren.

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PRINTED IN CANADA

EFFECTS OF LESIONS OF THE ROSTRAL THALAMUS ON BRAIN WAVES AND BEHAVIOR IN CATS [1]

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(Received for publication: May 15, 1958)

Cortical recruiting responses, first described in the anesthetized cat by Morison and Dempsey (1942), Dempsey and Morison (1942, 1943), and Morison and Bassett (1945), have been elicited by stimulating any of the following: the midline nuclei, the intralaminar nuclei including n. centrum medianum, n. ventralis anterior, n. reticularis, and at times the anterior nuclei (Jasper 1949, 1954; Hanbery and Jasper 1953; Starzl, Taylor and Magoun 1951). Strong stimulation of any one nucleus evokes responses in all other nuclei as well as the cerebral cortex (Hanbery and Jasper 1953; Starzl and Magoun 1951). Jasper has grouped these structures into a system variously called the diffuse projection system, non-specific thalamic projection system, or thalamic reticular system.

Studies on the organization of this diffuse projection system have revealed a topographical projection from individual nuclei to localized cortical areas (Hanbery and Jasper 1953; Jasper 1954). The corticopetal pathways seem to be independent of the thalamic relay and association nuclei, and apparently gather at the oral pole of the thalamus before reaching the cortex (Hanbery and Jasper 1953; Starzl and Magoun 1951; Verzeano, Lindsley and Magoun 1953). The n. ventralis anterior and the rostral n. reticularis may be the last station of this multi-synaptic system. Supporting evidences of such a final common path are the facts that stimulation of the rostral thalamus elicits recruiting responses with the shortest latency (Hanbery and Jasper 1953; Hanbery, Ajmone-Marsan and Dilworth 1954; Verzeano, Lindsley and Magoun 1953), and that retrograde degeneration of the intralaminar nuclei, n. ventralis anterior, and n. reticularis follows the ablation of either the cortex or the oral limb of the internal capsule (Nashold, Hanbery and Olszewsky 1955).

The nature of the recruiting responses elicited by stimulation of this system suggests that it plays an important role in the production of certain regular and bilaterally symmetrical rhythms seen in the human and animal electroencephalogram. However, except for the probable mediation of the spontaneous bursts in the electrocorticogram of animals under deep barbiturate anesthesia (Dempsey and Morison 1942, 1943), there has been no clear-cut demonstration of such a role. It has been suggested that recruiting responses and barbiturate bursts are comparable to the alpha rhythm in the human EEG (Jasper 1949; Bremer 1953), but recent studies relate them more to sleep spindles (Ralston and Ajmone-Marsan 1956; Hess, Koella and Akert 1953). The genesis of the 11 to 14 per sec. sleep spindles, like the recruiting responses and barbiturate bursts, is suspected by some investigators to depend, in part, on the thalamus (Jasper and Van Buren 1953; Henriksen, Grossman and Merlis 1949), and furthermore, the three types of potentials (recruiting responses, barbiturate bursts, and sleep spindles) are quite similar in their wave form and waxing-waning characteristics. Thus, they may have a common thalamic origin and the same final common path in the rostral thalamus.

[1] This study was supported by research grants, B-801(C1) from the National Institute of Neurological Diseases and Blindness, the National Institute of Health; the Fund for Neurobiology, Inc.; and the Wallace C. and Clara M. Abbott Memorial Fund of the University of Chicago.

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In addition to the recruiting responses elicited by low frequency stimulation of the diffuse projection system, a generalized desynchronization of the EEG follows high frequency (above 200 per sec.) stimulation. The latter is much like the EEG arousal obtained by stimulating the ascending reticular system in the brain stem (Starzl, Taylor and Magoun 1951; Magoun 1954; Moruzzi and Magoun 1949). Whether behavioral arousal, or EEG arousal, or both, depend on the intactness of the diffuse projection system, is not known. Similarly, although low frequency stimulation of the diffuse projection system produces an "arrest reaction" and prolonged stimulation produces sleep in unanesthetized cats (Hunter and Jasper 1949; Hess, Koella and Akert 1953), results of ablation studies are not conclusive to reveal its behavioral significance.

The present report deals with the EEG and behavioral effects following either electrolytic destruction or multiple-cutting of the rostral thalamus in cats. The first type of lesion was used to eliminate the final common path from the diffuse projection system to the cortex and the second type of lesion to disrupt the normal flow, but allow some isolated diffuse thalamo-cortical connections. Cats with either type of lesion were studied for the appearance of any alterations in arousal pattern, sleep spindles, barbiturate bursts, and recruiting responses in brain waves. In order to assess the functional significance of the diffuse projection system, the general behavior of these cats was observed and their ability to learn a visual discrimination, was tested.

METHODS

Fourteen adult cats were used as subjects. Preoperatively their behavior was observed and EEG's were recorded from 8 animals. After obtaining either normal sleep EEG's or sleep EEG's induced by barbiturate sedation, the animals were operated with aseptic precautions under pentobarbital sodium anesthesia. Johnson's stereotaxic apparatus was used to ablate the oral pole of the thalamus. Electrolytic lesions were placed at the frontal plane 12.0 according to the atlas of Jasper and Ajmone-Marsan (1954). A 24 gauge insulated nichrome wire with a 5 mm. exposed tip was used as the anode electrode. The tissue was destroyed using a direct current of 5 ma. for a period of 40 sec. Three to 6 punctures were made on each side of the midline. For the multiple transection, a special stylus and needle set made by Johnson Scientific Instrument Co. was employed. It consisted of a 20- or 19-gauge hypodermic needle with the lower end ground into an inverted V-shape. The upper end of the needle was attached with a metal piece indicating the side of V-shape opening. The stylus was made of piano wire with its lower end pre-bent into a 45° angle. The bent part measured 3 to 6 mm. in length. The upper end of the stylus was fitted with a metal piece to indicate the direction of the bent end. The stylus could be either withdrawn into the needle or pushed out to provide a cutting edge protruding to one side with a pre-determined length. The needle was attached to the electrode carrier of the stereotaxic instrument, placed inside the brain, and the stylus pushed out. By either moving the needle up and down or rotating it, a vertical or a horizontal section could be made subcortically. One puncture was made in each hemisphere at the position: frontal, 12.0 and lateral, 3.0. From this central position 6 vertical and 4 horizontal cuts were made anterior to the frontal plane of the puncture.

After the operation the animals were observed and EEG's were recorded at irregular intervals. Four of the cats were trained on a visual discrimination problem. Another 5 cats were used in a conditioned photic-driving study, the results of which will be reported elsewhere. For EEG recordings a Grass Model III four-channel machine was used. Needle scalp electrodes or electrodes made with fish hooks were placed at the two frontal and two occipital regions. In a few cases, wire electrodes insulated except at the tip were implanted through drill hole in the skull to record potentials directly from the cortex. Both bipolar and monopolar recordings with the indifferent electrode either at the vertex of the skull, or at the nose, or both combined, were routinely obtained. The cats were either restrained in an animal holder or left free in a wire cage. They were usually kept awake for 24 to 48 hours prior to the recording session. With such preparation, they usually fell asleep quite rapidly and seemed to be undisturbed by the scalp electrodes and lead wires. Sodium Pentothal or pentobarbital (20-40 mg/kg.) was given intraperitoneally to induce sleep in those animals failing to sleep spontaneously. It should be noted that we considered the tracings of spontaneous and barbiturate induced sleep to represent similar states, particularly with reference to the appearance of sleep spindles. Under both conditions, the spindles had the same frequency (11-16/sec.) in accord with Hess, Koella and Akert's (1953) thorough study of spontaneous sleep in the cat, and in both cases, the animals could be aroused electroencephalographically and behaviorally by a loud noise. The spindles seen in these two situations (spontaneous and barbiturate induced sleep)

were distinguished from the so-called barbiturate bursts. The latter appeared during barbiturate anesthesia from which the animals could not be aroused, were generally slower (6-8/sec.) than spindles [1], and tended to be monophasic in wave form while the sleep spindles were biphasic. No distinction was made between records obtained from scalp electrodes or implanted electrodes. On several occasions, tracings from both scalp and implanted electrodes were made simultaneously and little difference in the patterns was found when the different amplitudes were compensated. For visual discrimination training, a Y-shaped Yerkes box was used. The narrow end of the box was the starting point, and the wide end had two glass doors in which the stimuli were held. A black disc was the positive stimulus and a black square of the same surface area was the negative stimulus. The animal was trained to choose the positive stimulus by pushing open the correct door to receive a piece of meat. The door with the negative stimulus was locked. The non-correction method was used. The criterion of learning was 90 per cent correct responses within a 20-trial daily session. The training was completed within a day or two of the terminal experiment described below.

As soon as spindles re-appeared in the routine sleep tracings or after an arbitrarily long period in those cases where they did not re-appear, the cats were prepared for the study of recruiting responses. The skulls were opened under pentobarbital anesthesia and recording leads were placed on the sensory-motor area and the middle supra-sylvian gyrus bilaterally. Bipolar electrodes made of nichrome wire insulated except at the tips separated by 2 mm. were placed stereotaxically in the n. centrum medianum at the frontal plane 6.5. A Grass stimulator and isolation unit were used to deliver the shocks. Whenever a point yielded recruiting responses, it was coagulated with a 10 sec., 2 ma. anodal current. Additional pentobarbital usually was given at the end of the study to enhance the barbiturate bursts. Finally the animal was perfused with physiological saline and 10 per cent formalin, and the brain taken out for histological study. Coronal sections of 50 μ were cut serially through the brain. Every 10th section was stained with thionine. The extent of thalamic lesions were plotted with a projection microscope on outline drawings of the sections and the stimulating points identified. Postoperative survival of these animals ranged from 1 to 8 months.[2]

[1] This frequency was observed by us in several control cats without lesions. In the pertinent neurophysiological literature, the barbiturate burst is usually described as having a frequency of 8-12/sec. However, this difference may be more apparent than real. A careful perusal of a number of papers dealing with this phenomenon revealed that the frequency of the bursts in the sample records was nearly always around 8/sec. even though the texts described them as being 8-12/sec. Furthermore, some reports have assigned slower frequencies (5-10/sec.) to the barbiturate burst, including the original description of Derbyshire *et al.* (1936) and that of Clark and Ward (1944).

RESULTS

Complete multiple transection of the rostral thalamus. The rostral thalamus was transected completely in 3 cats (VA-9, 15, 20). The multiple cuts were not arranged evenly. They usually were surrounded by areas of gliosis of various extent. The damaged zones were the largest in cat VA-20; its rostral thalamus contained only a few isolated, intact areas. Some damage to the caudate nucleus and internal capsule was present, and the cuts reached the lateral geniculate body caudally in all 3 cats. Figure 1 gives the representative cross-sections through the lesions of the 3 animals.

Behaviorally, the cats showed spasticity of the hind legs, difficulty in walking, and a decrease of reactivity and motility after the surgery. (The term reduced reactivity was used to describe the slow, deliberate quality of the cats' movements, and the raised threshold of the cats' response to external stimuli.) They also showed what might be termed a catatonic reaction, i.e. they sat in one position for a long time, stared vacantly, could be put into bizarre postures, stopped in the middle of walking as though transfixed in the spot, and so on. They frequently walked into a corner of the room and stayed with their heads in it for hours without backing out. The cats had to be hand fed for a few days postoperatively. Cat VA-15 displayed left mydriasis. These signs disappeared within 14 days. The only lasting behavioral effects were some stiffness of the legs and slightly increased docility.

Cat VA-15 was trained on the visual discrimination and learned the problem in 360 trials and 133 errors.

EEG's were obtained during sleep and alert wakefulness preoperatively from cats VA-15 and VA-20. Figure 2A shows the sleep spindles in the preoperative EEG records of cat VA-20. Postoperative EEG results of the 3 cats are summarized in table I.

[2] We wish to express our appreciation to Mrs. F. Karapas and Mr. J. Asse for their help in the preparation of the histological materials.

A. *Activation of the EEG and behavioral arousal.*

Although the 3 cats were slow-moving and less responsive during the postoperative period, both EEG and behavioral arousal were easily obtained. Figure 2B shows the EEG arousal pattern of VA-20 recorded 5 days after surgery. The 5-8/sec. waves of relaxed wakefulness (Hess, Koella and Akert 1953; Bradley and Elkes 1957) were also present in the EEG of all animals.

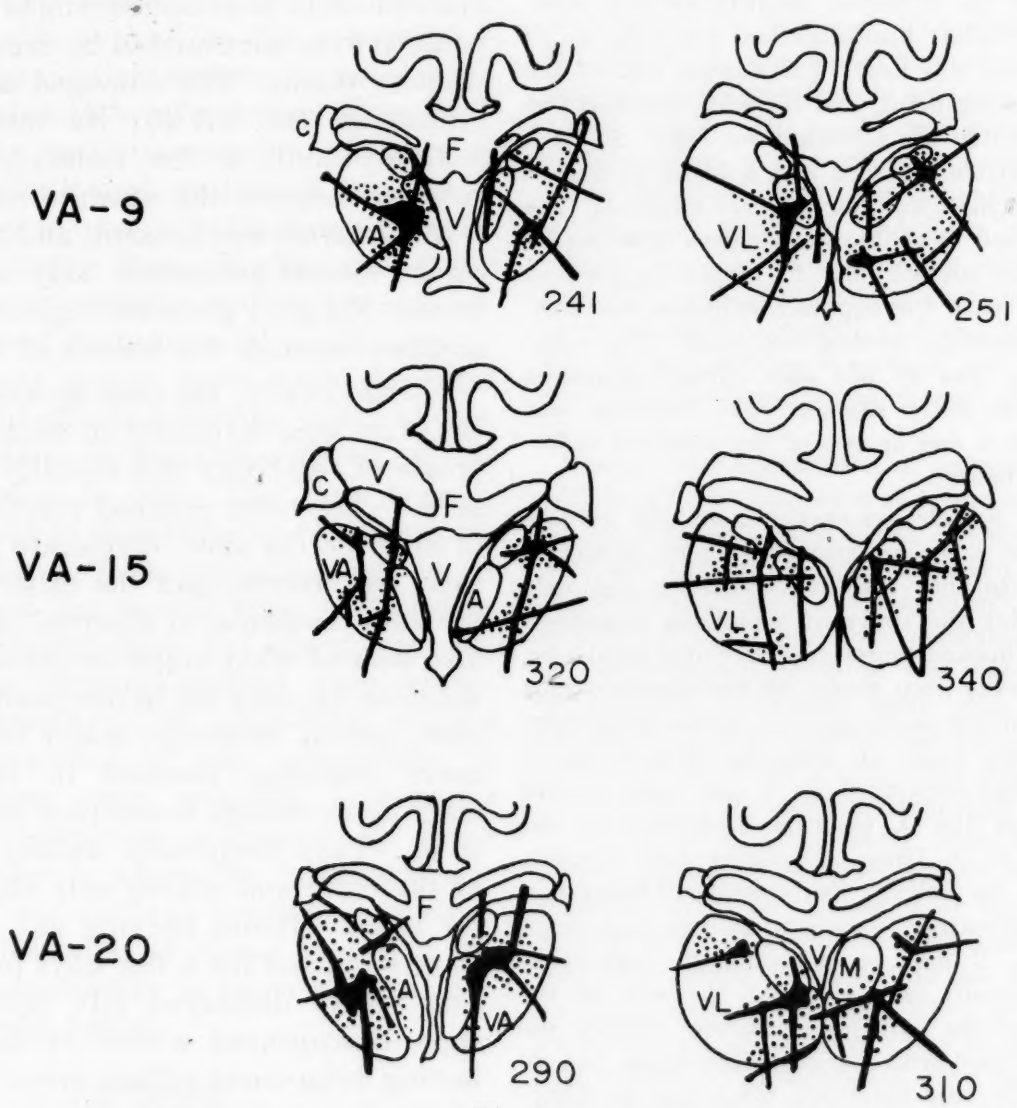


Fig. 1

Representative cross-sectional drawings through the rostral thalamus of three cats with multiple transections. Black line, complete cut; stippling, surrounding degenerated zone; A, anterior nuclei; C, caudate nucleus; F, fornix; M, medio-dorsal nucleus; V, ventricle; VA, n. ventralis anterior; VL, n. ventralis lateralis.

B. *Sleep spindles.*

Sleep spindles appeared about one month postoperatively in the records of cats VA-9 and VA-15, but were absent in sleep recordings on two and three instances before that time. Cat VA-20 did not show recognizable sleep spindles during the 3 month postoperative survival period. The appearance under Pentothal sedation of waves vaguely resembling sleep spindles at 92 days after surgery in this cat is shown in figure 2C. Figure 2D shows the arousal pattern taken during the same recording session, indicating that the barbiturate induced sleep EEG, like that of natural sleep, could be activated by a loud noise.

C. *Barbiturate bursts.*

Barbiturate bursts were seen in the EEG's of cats VA-9 and VA-20. No terminal experiment was performed on cat VA-15. The barbiturate bursts were abnormal. First, they

were poorly organized: the amplitude varied haphazardly and individual waves might be missing in a train of bursts. Second, they usually were confined to only one cortical lead instead of appearing in the entire cortex. Figure 2E shows the barbiturate bursts in the left occipital region of cat VA-20. In this cat, the bursts appeared more frequently in the left hemisphere than the right.

D. *Recruitment.*

Recruiting responses were obtained following stimulation of the n. centrum medianum in cats VA-9 and VA-20. Again these responses were not normal. They usually appeared more readily in the side ipsilateral to the stimulation, and in a poorly organized form without after discharges. Figure 2F shows barely recognizable recruiting responses in the left frontal region following stimulation of the left n. centrum medianum in cat VA-20. The activity in the right frontal region is mostly spontaneous and does not follow the stimuli consistently. On other stimulation, however, bilateral recruitment was occasionally obtained.

Complete transection of the rostral thalamus caused only short lived reversible behavioral effects, while the brain wave changes were long lasting. The brain wave effects included the suppression of sleep spindles from at least 25 to 92 days after surgery, and the occurrence of atypical, localized, barbiturate bursts and recruiting responses.

Complete electrolytic lesion of the rostral thalamus. The rostral thalamus was destroyed electrolytically in 5 cats. The lesion, similar in character to that reported by Carpenter and Whittier (1952), consisted of a central necrotic area and a surrounding zone of gliosis. The extent of the lesion varied from cat to cat, which in part resulted from the different number of punctures (3 to 6) placed into each hemisphere. Figure 3 shows representative cross-sections through the lesions of the 5 cats. Cat VA-21 had the smallest lesion, with only the very tip of the thalamus damaged. This lesion was exceptional also in that many apparently normal neurons were present within the degenerated area. The rostral thalamus of the remaining 4 cats (the rostral n. reticularis, the anterior nuclei, the midline nuclei, n. ventralis anterior, n. ventralis lateralis, and part of n. medialis dorsalis) was totally destroyed. Some apparently normal neurons could be found in n. reticularis and the midline nuclei only at the level of n. medialis dorsalis. The lesions of cat VA-7 and VA-14 extended posteriorly to the lateral geniculate body; and that of cat VA-10 extended ventrally to the dorsal part of the hypothalamus. The thalamic injury of all 5 cats also invaded, in different degrees, the head of the caudate nucleus and the internal capsule.

The postoperative behavioral changes following the rostral thalamic lesion were similar to those reported in the preceding section, but were more severe. All the cats showed spasticity of the hind legs, slowness in movement, decreased reactivity, catatonic reaction as was described earlier, and the tendency to stick their heads into a corner of the room. These symptoms gradually disappeared within from

TABLE I

Summary of postoperative EEG results of cats with complete transection of rostral thalamus.

Cat	Day EEG Arousal 1st Seen	Day Sleep Spindles 1st Seen	Terminal Experiment			
					Recruitment	
			Day	Bursts	Unilat.	Bilat.
VA-9	6	25	33	+?	+?	+?
VA-15	6	34	No Experiment performed			
VA-20	5	92?	94	+?	+?	+?

Numbers indicate number of days postoperatively when potentials first seen or terminal experiment performed. Question mark indicates abnormal appearance of potentials, see text. Plus or minus indicates presence or absence of bursts and recruitment.

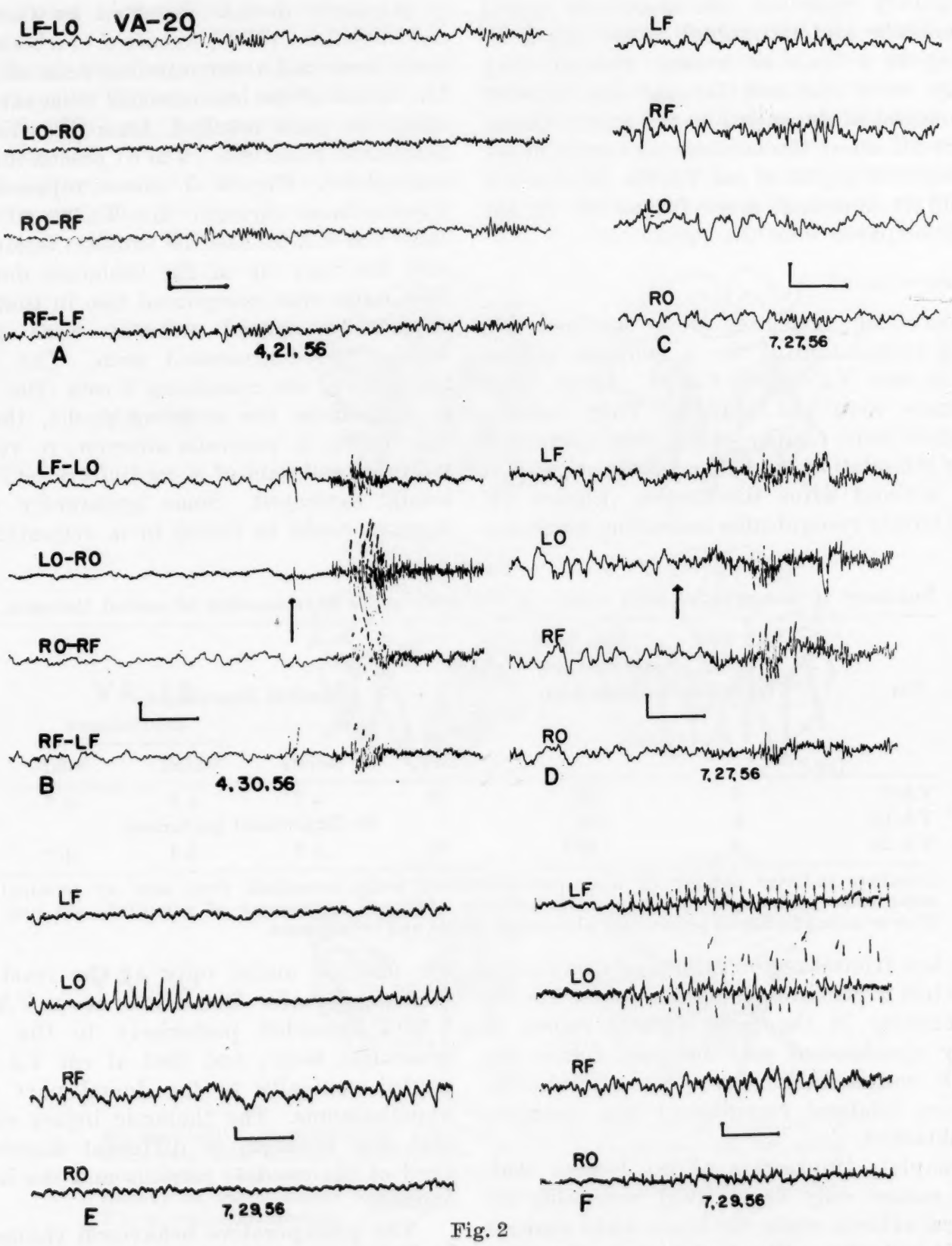


Fig. 2

EEG tracings of cat VA-20. Date of operation, 4-26-56. A, preoperative bipolar recording to show normal sleep spindles; B, arousal pattern in response to voice at arrow five days after surgery; C, brain waves vaguely resembling sleep spindles under Pentothal sedation; D, arousal pattern in response to voice at arrow under Pentothal sedation; E, localized, ill-formed barbiturate bursts; F, recruiting responses confined mainly to the left frontal region following 6 per sec., 3 V., 1 msec. stimulation of left n. centrum medianum; LF, left frontal; RF, right frontal; LO, left occipital; RO, right occipital; all calibrations, 50 μV. and 1 sec.

2 (VA-14, VA-21) to 8 weeks (VA-7, VA-10, VA-17). In addition, all animals had some difficulty in eating and swallowing for about 4 weeks. In the more severe cases (VA-7, VA-14, VA-17) the food had to be pushed into the back of the mouth before the animal would

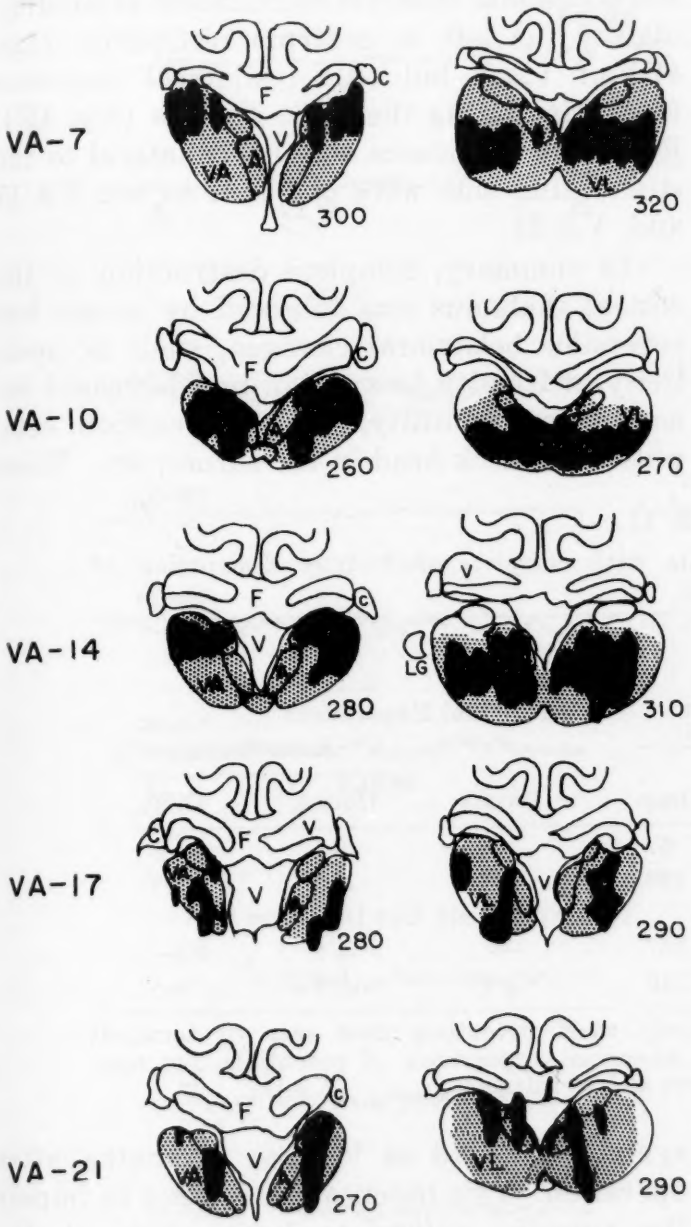


Fig. 3

Representative cross-sectional drawings through the rostral thalamus of five cats with electrolytic lesions. Black, central necrotic area; stippling, surrounding degenerated zone; A, anterior nuclei; C, caudate nucleus; F, fornix; LG, lateral geneculate body; V, ventricle; VA, n. ventralis anterior; VL, n. ventralis lateralis.

swallow it. The nictitating membranes of the animals, with the exception of VA-10, were kept in a half raised position after the operation for about 4 weeks. Cat VA-7 and VA-17 were completely prostrated for about 10 days, and cat VA-10 had a series of convulsions on the 6th and 7th postoperative days. The only lasting behavioral effects were a slight increase of docility, stiffness in walking, and possibly a slight decrease in reactivity.

Two of the cats were trained on the visual discrimination problem. Cat VA-17 learned the problem in 280 trials with 104 errors, and VA-21 learned it in 450 trials with 185 errors.

Preoperative EEG records were obtained from 4 cats, two recordings each from cats VA-7, VA-14, and VA-17, and four from VA-21. Normal alert, relaxed, and sleeping patterns with typical sleep spindles present in the latter were observed. No preoperative EEG tracings were obtained from cat VA-10. Figure 4A shows the preoperative records of sleep spindles obtained from cat VA-7 under Pentothal sedation. The postoperative EEG results of the 5 cats are summarized in table II.

A. *Activation of the EEG and behavioral arousal.*

Postoperatively all cats showed slow, high voltage waves during sleep, and eventually EEG arousal and the 5-8/sec. waves of relaxed wakefulness. The EEG arousal was observed within 10 days after surgery in 3 cats (VA-7, VA-17, VA-21), and on the 15th and 25th postoperative days respectively in cats VA-14 and VA-10. EEG's taken before that date in VA-10, VA-14, and VA-17 showed only high voltage waves, about 2-3/sec., even when the animals were behaviorally awake. Wakefulness was indicated by the animals' looking about, following moving objects with the eyes, etc. This transient suppression of EEG arousal and its dissociation from behavioral arousal appeared to occur only after total destruction of the rostral thalamus. Figure 4B shows EEG arousal from spontaneous sleep in cat VA-7 taken 7 days after operation.

B. *Sleep spindles.*

Sleep spindles were absent in the sleeping EEG of all 5 cats after operation. Furthermore, clearly recognizable spindles were never seen in the 5 cats during their entire postoperative survival period, i.e. 29 (VA-14), 66 (VA-7), 122 (VA-21), 136 (VA-10), and 167 (VA-17) days. Figure 4C taken from VA-7 66 days after surgery shows trains of

waves that vaguely resemble sleep spindles and with some imagination might be termed an abnormal manifestation of this wave form. However, whether one decides these waves are abnormal spindles or are not spindles at all, there is no question that they are markedly different from the typical, well defined sleep spindles seen in the preoperative records of this cat (fig. 4A). Cats VA-17 and VA-21, like VA-7, showed waves with a slight resemblance to sleep spindles at 167 and 114 days respectively after operation. No sleep spindles, abnormal or otherwise, were seen in many EEG tracings from these cats before these last dates.

C. *Barbiturate bursts.*

Barbiturate bursts did not appear in the terminal EEG recordings of cat VA-17, but were present in the records of VA-7, VA-10, and VA-21. These bursts were atypical in the sense that was discussed earlier, i.e. ill-formed and restricted to one cortical region at a time. Figure 4D shows the barbiturate bursts of VA-7. In this example the bursts are confined to the right occipital lead only. Cat VA-14 was not studied.

D. *Recruitment.*

Recruiting responses were obtained following stimulation of the n. centrum medianum in 4 cats. Cat VA-14 was not studied. These responses tended to be restricted to the stimulating side and usually with a poorly organized wave form without after discharge. Bilateral recruitment was obtained from stimulating the left n. centrum medianum of cat VA-10. Even in this case, however, the same site often yielded only ipsilateral recruitment during other periods of stimulation. There was occasional bilateral recruitment after stimulating the left n. centrum medianum (fig. 4E) of VA-7, but only ipsilateral responses from stimulating the right nucleus (fig. 4F). Recruiting responses mainly ipsilateral to the stimulating side were obtained in cat VA-17 and VA-21.

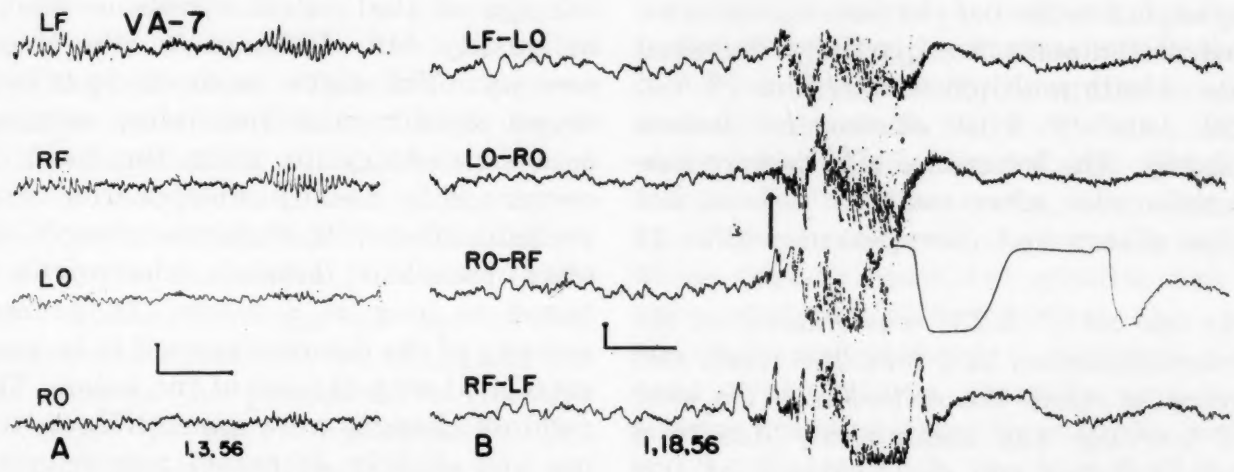
In summary, complete destruction of the rostral thalamus was followed by severe but reversible behavioral changes; such as, spasticity, difficulty in swallowing, decreased reactivity and motility, catatonic reaction, compulsion to stick head in the corner, etc. These symptoms lasted as long as 2 months after operation. This lesion appeared not to impair the animals' ability to learn a visual discrimination. EEG effects following such a lesion were similar to that reported above for the complete transection of the rostral thalamus but were more severe and prolonged. The complete suppression of the sleep spindles lasted as long as 5 months after surgery. Both barbiturate bursts and recruiting responses were either absent or present only in restricted cortical regions and in atypical form. In addition, there was a dissociation of EEG and behavioral arousal up to 4 weeks after the surgery in some cats.

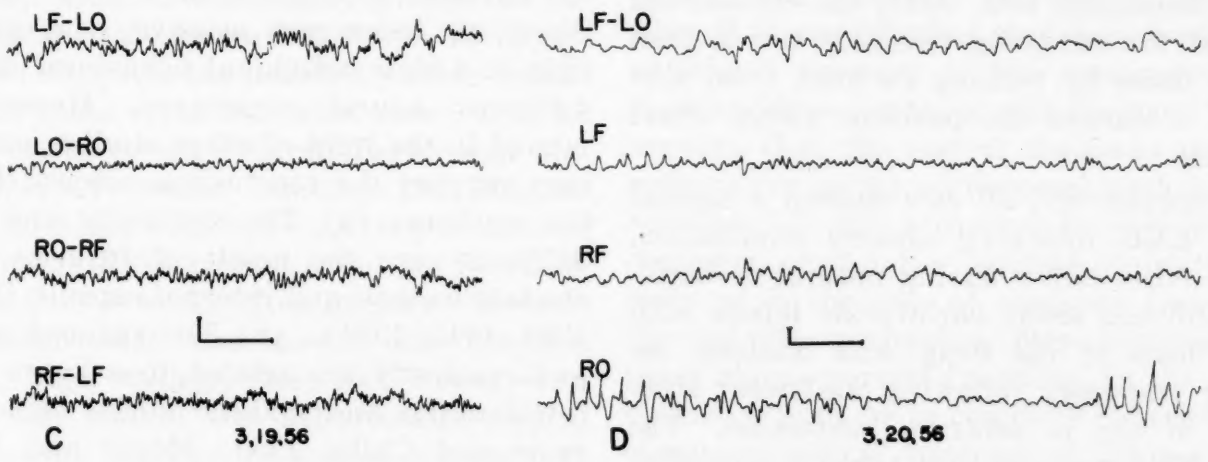
TABLE II

Summary of postoperative EEG results of cats with complete electrolytic destruction of rostral thalamus.

Cat	Day EEG Arousal 1st Seen	Day Sleep Spindles 1st Seen	Terminal Experiment			
					Recruitment	
			Day	Bursts	Unilat.	Bilat.
VA-7	7	66?	67	+?	+?	+?
VA-10	25	Not Seen	136	+?	+?	+?
VA-14	15	Not Seen	No Experiment, Cat Died Day 29			
VA-17	9	167?	167	—	+?	—
VA-21	7	114?	122	+?	+?	—

Numbers indicate number of days postoperatively when potentials first seen or terminal experiment performed. Question mark indicates abnormal appearance of potentials, see text. Plus or minus indicates presence or absence of burst and recruitment.





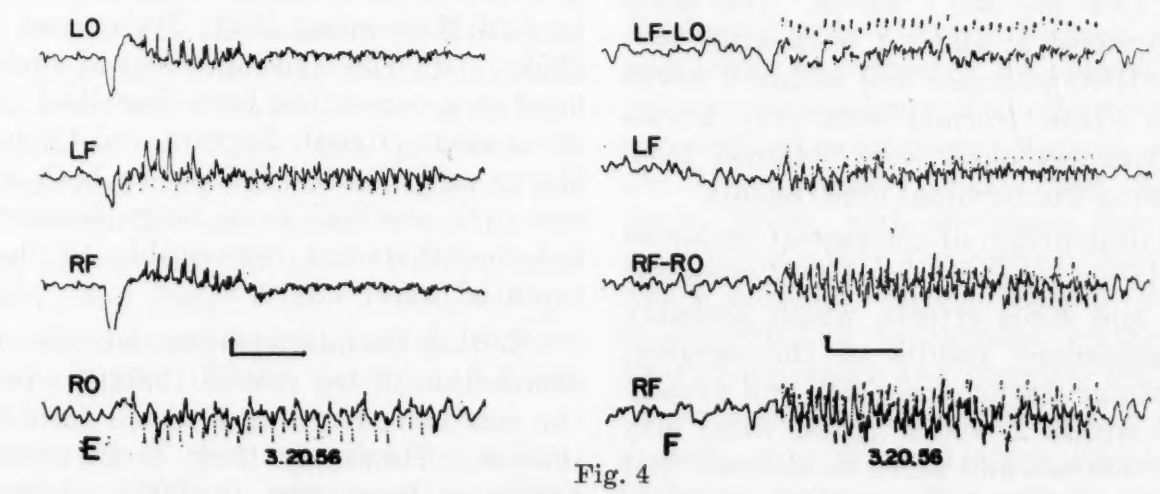


Fig. 4

EEG tracings of cat VA-7. Date of operation, 1-11-56; A, preoperative monopolar recording to show sleep spindles obtained under Pentothal sedation; B, arousal pattern in response to voice at arrow seven days after surgery; C, brain waves vaguely resembling sleep spindles under Pentothal sedation; D, localized ill-formed barbiturate bursts; E, recruiting responses following 6 per sec. 8 V., 1 msec. stimulation of left n. centrum medianum; F, ipsilateral recruiting responses following 8 per sec., 10 V., 1 msec. stimulation of right n. centrum medianum; LF, left frontal; RF, right frontal; LO, left occipital; RO, right occipital; all calibrations, 50 μV. and 1 sec.

Partial destruction of the rostral thalamus. The rostral thalamus was partially damaged in 6 cats: 4 with multiple transections (VA-3, 4, 8, 23) and 2 with electrolytic lesions (VA-12, 16). The behavioral effects were similar to those seen after complete lesions, but much less severe and disappeared within 14 days.

Only one cat (VA-23) was trained on the visual discrimination and took 560 trials and 285 errors to reach the criterion. This slow rate of learning was undoubtedly due to a visual field defect and the tendency of this cat to make left turns. For the first 350 trials, it consistently chose the left door in the discrimination box. After the cat learned to inhibit the left-going tendency and to scan the two doors by turning its head from side to side, it learned the problem within about 200 trials.

Postoperatively, all cats showed a normal arousal EEG following sensory stimulation, sleep spindles either during natural or barbiturate induced sleep, barbiturate bursts with higher doses of the drug, and bilateral recruiting responses following unilateral stimulation of the n. centrum medianum. The earliest EEG tracings were taken 5 days after the operation in 2 cats. In both cases, there were both normal alert (20-40 per sec.) and relaxation (5-8 per sec.) waves. The sleep spindles appeared at about 1 week after surgery in the EEG of 2 cats and within 3 weeks in the other 3 cats. Normal barbiturate bursts and recruiting responses were obtained from all cats during the terminal experiments.

Partial destruction of the rostral thalamus plus its adjacent regions caused only transient behavioral and EEG effects, which probably reflected secondary results of the surgery, edema, vascular disturbance, etc., and usually cleared up within 2 weeks. These cases may be used as controls and serve to indicate that the results reported in the preceding sections are long lasting postoperative effects of specific lesions and not of destroying *any* subcortical region.

DISCUSSION

Behavior. Reversible behavioral changes following either incomplete or complete damage of the rostral thalamus are similar in quality but different in the degree of severity. The signs, such as spasticity, reduced motility and reactivity, catatonic reaction, tendency to stick the head into a corner, etc., usually disappeared within 2 weeks in those with thalamic transections, but after complete thalamic electrolytic lesion lasted as long as 8 weeks. In general, the severity of the disorder seemed to be positively correlated with the size of the lesion. The only residual changes were some stiffness in walking and slightly decreased reactivity and increased docility. The last mentioned is a very common behavioral change following increased nursing care after any brain surgery. Since our lesion was massive, it is not possible to assign individual behavioral items to different neural structures. However, if viewed in the light of other studies, our findings support the conclusions reached by earlier authors: (*a*) The spasticity and motor difficulty are the result of injuries to the caudate nucleus and internal capsule (Mettler 1944, 1945, 1951). (*b*) The reduced motility and reactivity are related to a lesion in the intralaminar and midline nuclei (Knott, Ingram and Chiles 1955; Meyer and Hunter 1952; Schreiner, Rioch, Pechtel and Masserman 1953). (*c*) Docility follows destruction of the anterior nuclei (Schreiner, Rioch, Pechtel and Masserman 1953; Meyer and Hunter 1952). (*d*) The striking effect of sticking the head in a corner has been described in 2 previous cases (Knott, Ingram and Chiles 1955; Meyer and Hunter 1952). In both cats this sign was ascribed to a large destruction of anterior thalamus comparable to the lesion reported here.

Neither complete transection nor complete destruction of the rostral thalamus prevented the cats from learning a visual form discrimination. However, they took more trials (ranging from 280 to 560) to learn the problem than normal cats (average 180 trials, unpublished data). Whether such a slower rate of learning is a result of thalamic lesion (Schreiner, Rioch, Pechtel and Masserman 1953), or is secondarily induced from other behavioral changes (i.e. visual field defect, difficulty in walking and turning around)

needs further clarification. In general, the present results demonstrate the reversible nature of the behavioral effects following rostral thalamic lesion, indicating a high degree of vicarious functioning within the thalamus, and the not indispensable role of the hypothesized final common path of the diffuse projection system for normal behavior in cats.

EEG. Partial damage of the rostral thalamus caused practically no change in the EEG as soon as the postoperative recovery period (about 14 days) was passed. The effects following complete transection or complete destruction were similar but more severe and long lasting after the latter type of lesion. The EEG arousal was usually present at the first postoperative recording (3 to 10 days). This fact supports the possibility of an extrathalamic route from the brain stem reticular system to the cortex (Starzl, Taylor and Magoun 1951; Verzeano, Lindsley and Magoun 1953). In 3 cats with large electrolytic lesions, however, the EEG arousal could not be elicited until 2 to 4 weeks after surgery. Records taken before that time showed only low frequency, high voltage, sleep-like waves even though the animal was behaviorally awake. These results confirm the earlier reports that slow waves usually dominate the EEG in waking cats following thalamic lesions (Knott, Ingram and Chiles 1955; Meyer and Hunter 1952). The dissociation of EEG and behavioral arousal following rostral thalamic lesion indicates once again the not invariable correspondance of EEG and behavior in wakefulness and sleep. Other examples of this type of dissociation are as an effect of the injection of atropine in cats (Bradley and Elkes 1957) and dogs (Wikler 1952), and appearing after a prolonged period without sleep in the human (Blake, Gerard and Kleitman 1939).

The absence of sleep spindles was a consistent and striking postoperative EEG change following rostral thalamic lesions. The waking EEG shifted into high voltage, sleep waves without spindles occurring in the intermediate stage, where they were most easily seen preoperatively, or in any other portion of the record. However, apparently normal spindles quickly re-appeared in all the cats with partial lesions and after longer periods in 2 of the cats with complete transection. On the other hand, easily recognizable spindles were never seen in the 5 cats with complete electrolytic destruction of the rostral thalamus. In 3 of these cats, after long postoperative periods, waves eventually appeared which vaguely resembled spindles, but which were markedly different from the spindles observed preoperatively. Although on the basis of the criteria generally used to characterize spindles, these wave forms could not be classified as such, the fact that they did not seem to be present in earlier postoperative recordings suggests that they represented a partial and abnormal recovery of spindling. Also, it is possible that they may have shown additional recovery if the postoperative periods had been extended still further. Thus, it appears that the rostral thalamus may normally serve as the corticopetal path for sleep spindles. If this structure is only partially damaged, or if a few isolated connections remain as in the case of complete transection, the spindle mechanism may eventually recover almost normal function. In the absence of such a path, as in complete electrolytic destruction, normal function of the mechanism is not recovered, but atypical spindles, after a long period, may be produced via an alternate pathway or by the cortex alone independent of subcortical influences. This latter possibility is suggested by observations of a certain independence of simultaneous thalamic and cortical recordings (Morison and Dempsey 1942; Jasper 1949; Hess, Koella and Akert 1953), with the sleep spindles being more prevalent in the cortical tracings. Also, waves similar to the barbiturate bursts have been identified in isolated cortex (Bremer 1953; Kristiansen and Courtois 1949).

Both barbiturate bursts and recruiting responses were affected after complete rostral thalamic damage. The effects were rather similar, i.e. usually the waves appeared in various, localized cortical areas, were variable in amplitude, and occasionally missed a response in a train. The recruiting responses were not followed by after discharges. These results support the supposition of Dempsey and Morison that these 2 types of

response depend on the thalamus. Since some barbiturate bursts and recruiting responses may be obtained in the absence of the anterior half of the thalamus, the final common path suggested for the thalamic diffuse projection system through the rostral thalamus may not be the only corticopetal route for these potentials. Some alternative, albeit less efficient, pathways must transmit recruiting influences from structures posterior to the rostral thalamus to the cortex. The present results also suggest that both the barbiturate bursts and the recruiting responses are more closely related to sleep spindles than to alpha rhythm. First, these three types of potentials are all affected by rostral thalamic ablation indicating that they may be mediated through a common neural system or systems. Second, they are all electrical signs of decreased functional activity of the brain, i.e. sleep, anesthesia, and induced hypersynchrony,[1] whereas the alpha rhythm reflects the electrical activity of the brain during normal wakefulness.

SUMMARY

The EEG and behavioral effects following rostral thalamic lesions were studied in 14 cats; 3 with complete transection, 5 with complete electrolytic lesions, and 6 with partial destruction.

Behavioral effects following either complete transection or complete destruction of the rostral thalamus were similar in quality, but different in the degree of severity. The signs and symptoms were: spasticity, difficulty in walking and swallowing, reduced motility and reactivity, catatonic reaction, tendency to stick the head in a corner, and so on. These changes could last from 2 to 8 weeks. The only residual effects were some spasticity of the legs and a slight increase of docility. Cats with rostral thalamic destruction could learn a visual form discrimination.

EEG effects following either complete transection or complete destruction of the rostral thalamus were again similar in quality but different in the degree of severity. (*a*) The arousal pattern could be elicited within from 3 to 25 days after surgery. As shown by 3 cats with massive lesions, EEG arousal could be absent during behavioral arousal. (*b*) The sleep spindles were either absent throughout the postoperative survival period or might have recovered to some slight extent within 3 (transection lesion) or 5 (electrolytic lesion) months. (*c*) Both barbiturate bursts and recruiting responses were seen to be affected at the terminal experiment, i.e. restricted to localized cortical areas and poorly organized in form.

Partial damage to the rostral thalamus caused only transient and slight behavioral and EEG changes in the immediate postoperative period.

The results are discussed in relation to the thalamic role in behavior and the functional significance of the final common path from the thalamic diffuse projection system to the cortex.

RÉSUMÉ

Chez 14 chats les effets électroencéphalographiques et les altérations du comportement consécutifs à une lésion rostrale thalamique sont étudiés. Trois chats avaient une transection totale, 5 présentaient des lésions électrolytiques complètes, et 6 avaient des destructions partielles. Les effets sur le comportement après transsection complète ou destruction complète de la partie rostrale du thalamus étaient similaires en qualité; mais variaient tant qu'au degré de sévérité. Les symptômes étaient: spasticité, des difficultés de la démarche et de la déglutition, une motricité réduite et une réactivité réduite, une réaction catatonique, une tendance à cacher la tête dans un coin, etc. Ces changements pouvaient durer de 2 à 8 semaines. Les effets permanents étaient un certain degré de spasticité des membres et une légère augmentation de do-

[1] Evarts and Magoun (1957) have reported the elicitation of recruiting responses in the alert, wakeful cat. However, it is still a moot question as to whether cerebral function remains optimal during the few seconds of recruitment, or for that matter during the much longer periods of EEG and behavioral dissociation mentioned in this paper and elsewhere (Wikler 1952; Bradley and Elkes 1957). More intense stimulation of the diffuse projection system in the waking animal as carried out by Hunter and Jasper (1949) elicited an "arrest" reaction. In other instances of hypersynchrony as typified by petit mal seizures, there is little question of the functional depression of the brain.

cilité. Les chats qui présentaient une destruction thalamique rostrale pouvaient apprendre une forme de discrimination visuelle. Les effets électroencéphalographiques qui suivaient, soit une transsection complète soit une destruction complète de la partie rostrale du thalamus, de nouveau étaient similaires en qualité, mais variaient quant au degré de leur sévérité.

a) La réaction d'arrêt pouvait être obtenue à partir de 3 jours jusqu'à 25 jours après l'opération. Trois chats avec des lésions massives montraient une activation du comportement sans activation électroencéphalographique concomitante.

b) Les fuseaux du sommeil étaient soit absents pendant toute la période post-opératoire ou pouvaient revenir après 3 semaines (après transsection) ou 5 mois (lésions électrolytiques).

c) Pendant l'expérience terminale aiguë, les fuseaux, électroencéphalographiques barbituriques et les réponses de recrutement étaient influencés: c'est-à-dire, elles ne se présentaient que dans des aires corticales localisées et étaient mal organisées. Une destruction locale de la partie rostrale du thalamus ne provoquait que des variations passagères et légères du comportement et de l'EEG pendant la période post-opératoire immédiate.

Ces résultats sont discutés en rapport avec le rôle du thalamus sur le comportement et la signification fonctionnelle de la voie commune finale du système thalamique diffus de projection au cortex.

ZUSAMMENFASSUNG

Veränderungen im EEG und im Verhalten, welche nach rostralen thalamischen Läsionen auftreten, wurden bei 14 Katzen untersucht. Drei dieser Tiere hatten eine komplette Querdurchschneidung des rostralen Thalamus, 3 hatten totale elektrolytische Zerstörungen und 6 hatten partielle Läsionen.

Veränderungen im Verhalten nach kompletter Durchschneidung oder totaler Zerstörung des rostralen Thalamus waren qualitativ ähnlich, jedoch bestanden Unterschiede im Grad der Veränderungen. Folgende Symptome wurden beobachtet: Spastizität, Gehstörungen, Schwierigkeiten im Schlucken, Bewegungsverminderung, verminderte Reaktivität, katatonische Reaktionen, eine Tendenz den Kopf in eine Ecke zu stecken, u.a.m. Diese Veränderungen dauerten manchmal zwei bis acht Wochen an. Die einzigen Residualsymptome waren aber eine gewisse Steifheit der Glieder und eine gewisse Steigerung der Zahmheit. Katzen mit rostraler thalamischer Zerstörung waren fähig, visuelle Diskriminationsteste zu erlernen.

EEG-Veränderungen nach totaler Durchschneidung oder Zerstörung des rostralen Thalamus waren ebenfalls ähnlich in qualitativer Hinsicht, aber verschieden im Grad ihrer Schwere. Die Weckreaktion konnte innerhalb einer Periode von 3 bis 25 Tagen nach der Operation wieder hervorgerufen werden. Drei Katzen mit massiven Läsionen zeigten, dass die Weckreaktion im EEG fehlen konnte, obwohl ein Weckeffekt im Verhalten vorhanden war. Die Schlafspindeln fehlten entweder während der ganzen postoperativen Überlebenszeit oder erholten sich zu einem gewissen Grad wieder nach drei Monaten bei Tieren mit einer thalamischen Durchschneidung oder in 5 Monaten bei Tieren mit einer elektrolytischen Zerstörung. Im terminalen Experiment waren die Barbituratspindeln und rekrutierenden Antworten eingeengt auf umschriebene Rindenfelder und mangelhaft organisiert.

Teilweise Zerstörung des rostralen Thalamus erzeugte nur vorübergehende und geringfügige Veränderungen im Verhalten und im EEG, welche nur während einer kurzen Periode unmittelbar nach der Operation nachgewiesen werden konnten.

Die mitgeteilten Befunde werden besprochen in Bezug auf die Bedeutung des Thalamus für das Verhalten und in Bezug auf die funktionelle Bedeutung der gemeinsamen Endbahn des diffusen thalamo-kortikalen Projektionssystems.

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PRINTED IN CANADA

ELECTROCORTICAL MANIFESTATIONS OF EPILEPSY IN MONKEY [1]

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(Received for publication: June 9, 1958)

INTRODUCTION

It has been shown in previous work on cortical epileptogenesis in monkeys that there is a definite pattern of distribution of the excitability of the cortex to convulsions induced by direct electrical stimulation (French *et al.* 1956). The precentral "motor" areas had the lowest and the occipital cortex the highest threshold for seizure induction, with the frontal lobe, anterior temporal pole and parietal cortex occupying an intermediate position in the gradient of excitability (fig. 1).

It was also shown in a following paper (Livingston *et al.*) that the partial isolation, by subpial circumsection without undercutting, of a segment of the motor cortex induced changes both in the excitability and capacity for seizure spread from the area so prepared, as well as from the area exactly homotopic to it in the contralateral hemisphere, although this latter region had not been interfered with directly in any form. Moreover, this contralateral homotopic area showed spontaneous spiking and an increased capacity for seizure induction after the operation.[4]

The purpose of the experiments reported here was to explore the nature of the phenomena underlying the different excitability of various cortical areas as well as those responsible for the enhancement of excitability in the area homotopic to a chronically circumsected cortical locus. A lead was provided by Abdullah and Magoun's (1957) finding that seizures induced either by Metrazol or high frequency electrical stimulation of the cortex in cats interfered with potentials evoked by local cortical stimulation which, according to one proposal, are due to dendritic activity in the cortex (Chang 1951, 1952). A close relationship between dendritic depolarization and seizure discharges has also been proposed by Brazier (1955) who suggests that epileptic spikes might be generated in the apical dendrites of the cortex.

To assess the role of dendritic depolarization in epileptogenesis, preliminary studies were made in monkeys of cortical responses evoked by stimulation of the thalamic relay nuclei (augmenting response), of the diffusely projecting thalamic nuclei (recruiting response), of contralateral surface loci (callosal response) and of local surface loci (local or direct cortical response). The last were found to be most easily handled and consistent and, since they have been shown to indicate dendritic activity, were selected for this study.

METHODS

The experiments reported here were made on 14 monkeys (*Macaca mulatta*). In 11 of these, subpial circumsection of an area of cortex approximately 1 square centimeter was made either in the motor or premotor cortex of one hemisphere by a procedure described in detail elsewhere (Livingston *et al.*). All animals had recovered full vigor when the definitive experiment was made 10-30 days later. When made in the motor cortex, the circumsection was always placed in the arm area so that observations could be standardized. These monkeys displayed slight to moderate distal brachial monoparesis postoperatively, usually with complete recovery after a few days.

For the definitive experiments, terminal evaluation in operated animals and control examination in 3 unoperated monkeys, tra-

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[4] We shall apply herefrom the term *homotopic* to that area which is symmetrically placed in the opposite hemisphere, to a circumsected locus.

cheotomy and bilateral craniectomy were performed under ether anesthesia and the head was secured in the stereotaxic frame. Craniectomy was necessarily extensive and all of the cerebral convexity was exposed except for the anterior part of the temporal and inferior temporo-occipital regions. Flaxedil ® was administered intravenously (10 mg/hour, average dose), respirations being maintained artificially.

Monophasic square pulses (0.01 - 0.03 msec., 20-120V.) were delivered from a Grass S4-C stimulator and isolation unit through a concentric pair of stainless steel electrodes with 1 mm. tip-barrel distance. The tip was made to penetrate the cortex until the bared end of the barrel contracted the cortical surface. The barrel was always the cathode.

Recording was uniformly monopolar-differential, employing a balanced pair of leads, on each wound margin as reference. The pick-up electrode was a chlorided-silver ball resting lightly on the surface 3 mm. away from the stimulating electrodes. Another chlorided-silver ball electrode was placed 2 mm. away from the recording electrode and led off to ground to minimize stimulus artifacts. Responses evoked by single shock stimuli were delivered through two Grass P_5 RC coupled preamplifiers to a DuMont 333 double-beam cathode-ray oscilloscope where they were photographed with a Grass recording camera. The frequency-response band of the preamplifiers was set for each response so as to minimize interference without distortion of the signal.

To obtain more complete information concerning differences in the responses obtained in the various areas studied, current intensity was progressively increased while the duration of the pulses remained unchanged. Data so obtained permitted plotting of strength-response curves (fig. 3), the abcissae representing intensity of current and the ordinate indicated baseline-to-peak amplitude of the responses. The effect of voltage increments upon latency of response was also measured and plotted in the same way. In a few cases recordings of the spontaneous ECG activity were made from multiple loci over the convexity by means of a Grass Model III amplifier and inkwriter.

Recording sites selected for study were widely disseminated over both hemispheres from occipital to frontal pole in all experiments, always symmetrically opposed points were studied in each animal. Particular attention was directed to the effect of the preliminary operative intervention upon responses in the cortical locus circumsected and in that area homotopic to it on the contralateral motor or premotor cortex. In these experiments bilateral responses were recorded

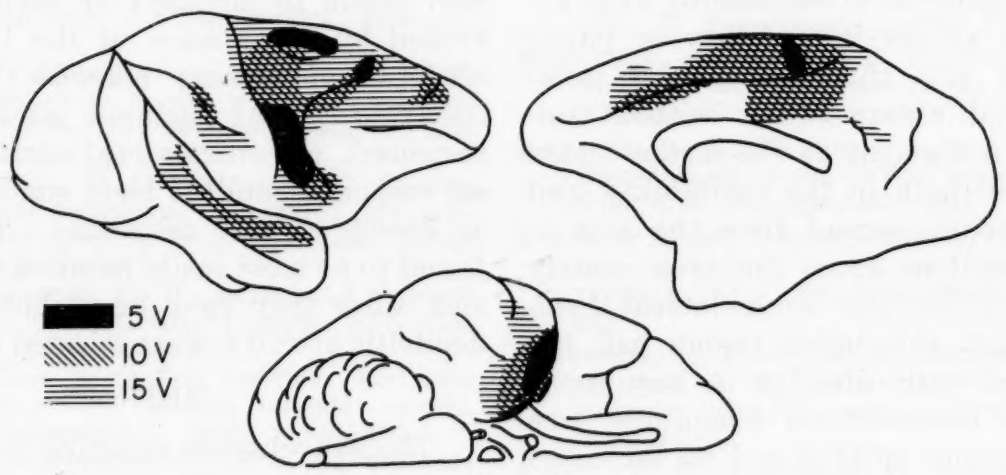


Fig. 1

Diagrams of the monkey brain show the difference in threshold voltages for electrically-induced seizures in various cortical areas (From French, Gernandt and Livingston 1956).

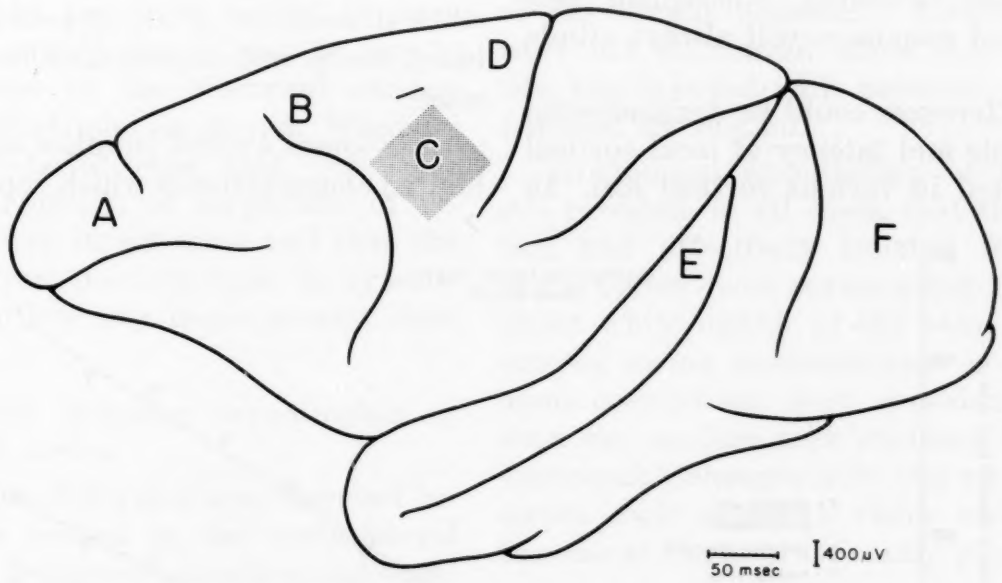
before and after surgical division of the corpus callosum in order to assess possible tonic influences mediated by callosal systems upon dendritic depolarization. Comparable assessments of induced homotopic depolarizations were made after the circumsected zone was injected with 2 per cent procaine, undercut or removed.

cortical cells. The completeness of the corpus callosum section was also verified.

RESULTS

(a) *Animals without a previous circumsection*

The appearance of the local cortical response exhibited some features of similarity



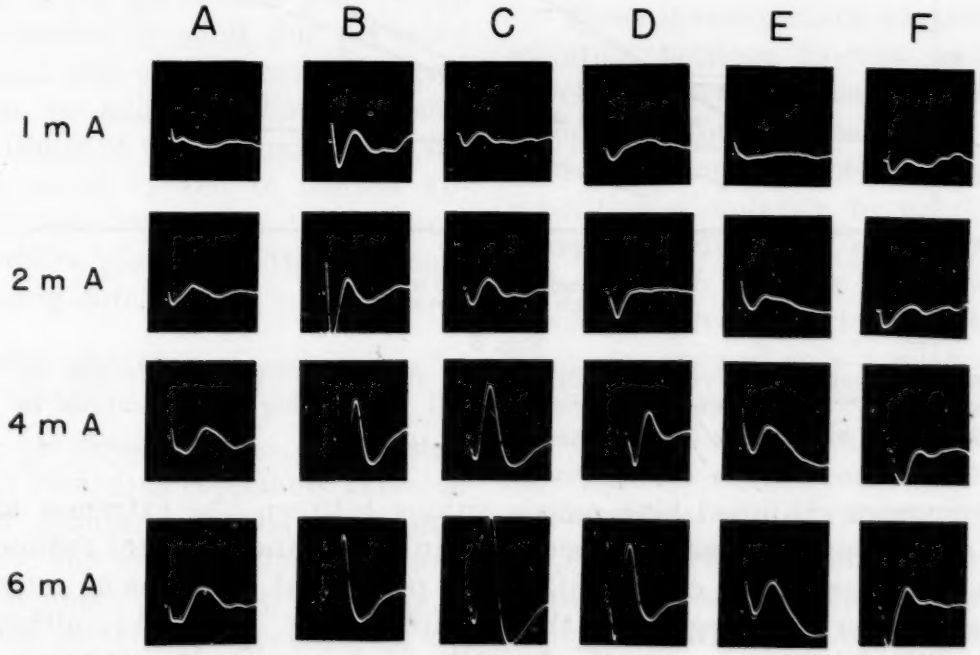


Fig. 2

Records of local cortical responses taken in points of A to F on the cortex of a single animal. Stimulation intensities were the same in all areas (0.01 msec. single shocks). The shaded zone C indicates a point homotopic to a circumsection on the opposite hemisphere.

At the termination of each experiment, serial sections of the circumsected locus were studied in order to determine the extent of the cuts and the integrity of the remaining

wherever evoked on the cortical surface although important variations, to be described later, were striking. An initial positive deflection, which commonly increased in amplitude

with increments in voltage, consistently followed the shock artifact. This wave was succeeded immediately by a negative deflection which always exhibited greater magnitude and duration. Irregularities in the decline of this response occasionally occurred but no other consistent events were discernible. Clearly, the negative deflection was dominant, and unless otherwise indicated, subsequent reference to evoked responses will always allude to this wave.

Marked differences could be demonstrated in the amplitude and latency of local cortical responses elicited in various cortical loci. In the motor area responses exhibited high amplitude and short latency and the magnitude of responses in the arm area were consistently higher than were those in other regions of the motor cortex (fig. 2C). The average amplitude of responses evoked here was 1000 μV. when tested to maximal shocks, while comparable potentials elsewhere in the motor cortex rarely exceeded 800 μV. (fig. 2D). These negative deflections in the motor cortex appeared as narrow-based high waves which reached peak amplitude 8-12 msec. after the stimulus artifact. Additionally motor cortical responses characteristically exhibited lower thresholds and steeper strength-response curves than did those recorded from other regions (fig. 3).

Contrasting sharply with potentials evoked in the motor cortex were those elicited in the occipital region (fig. 2F). Here thresholds were high and the negative deflection rarely achieved an amplitude of 300 μV. The wave, when it occurred at all, appeared as a broad-based hump with a peak-time latency of 20-25 msec.

Responses evoked in other cortical loci exhibited characteristics which represented transitions between the extremes of those elicited in motor and occipital regions. Commonly, the prefrontal area was as unexcitable as the occipital pole (fig. 2A), although, occasionally, high amplitude responses were recorded particularly near the anterior end of the arcuate sulcus. The postcentral gyrus, parietal cortex and posterior-superior temporal regions were slightly more responsive (fig. 2E). The premotor and frontal oculomotor regions were distinctly more excitable (fig. 2B). Here, responses approached in latency and appearance those elicited in the

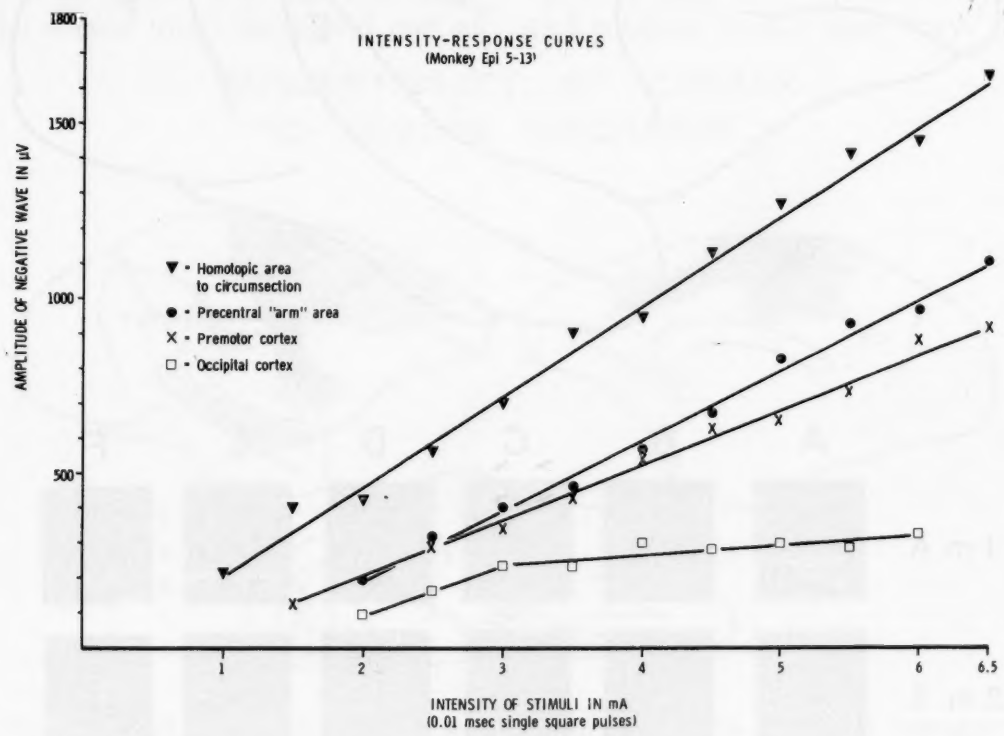


Fig. 3

Intensity-response curves show differences in excitability of four loci on the cortex. Note that homotopic point C showed highest amplitude in response to all stimuli.

motor cortex although amplitudes rarely exceeded 600 μV.

In each preparation responses were obtained always at symmetrically opposite loci in both hemispheres, so that each series of responses had its own internal control. This was done as the only possible means of securing some reliability in the data, since the absolute amplitudes of the responses tended to vary from animal to animal, due at least in part to minor differences in the electrical characteristics of the electrodes employed. What we considered significant was that the same pattern of distribution of amplitude of response was present in all cases and that the difference between the responses on symmetrically opposite loci was never greater than 10 per cent.

(*b*) *Animals with previous circumsection of the premotor cortex*

No consistent difference was observed between responses evoked in the contralateral area homotopic to the circumsection and those elicited in neighboring cortex. Inside the circumsected area itself potentials were often difficult or impossible to elicit due probably to the trauma and scar of the previous operation. There was no evidence that responses could cross the limits of the circumsection, for potentials were never evoked to stimuli applied either outside or inside the cortical island by electrodes placed on the alternate side of the existing cuts.

(*c*) *Animals with previous circumsection of the motor cortex*

Confirming previous results (Livingston *et al.*), inkwriter recording commonly revealed the presence of spontaneous fast, low amplitude spiking in the circumsected area and from a point homotopic to it contralaterally.

Except in one instance, no consistent, recognizable, local cortical responses were obtained when both the stimulating and recording electrodes were placed inside the limiting cuts. The exceptional case displayed moderately low amplitude responses with latencies comparable to those exhibited by unoperated segments of motor cortex.

In all experiments, striking changes appeared in the contralateral area homotopic to the circumsected motor cortex. The local cortical responses at this site were consistently higher in amplitude than were potentials evoked either at the same site in control animals or in the adjacent leg and face areas (fig. 2, 3). There was no appreciable change in the latency of these responses. These augmented responses were unchanged by section of the corpus callosum. Additionally, they were not influenced when the circumsected site was injected with procaine, undercut or removed by suction.

Anatomical examination of the operated site revealed, in all cases, that the circumsection had effectively isolated the island of motor cortex from surrounding tissue leaving intact white matter at the base. In some instances, owing to hemorrhage and scar, these basal connections were considerably smaller than the surface area enclosed by the cuts. Comparable changes were also apparent in the cortex itself, although viable and apparently functional tissue prominently persisted.

DISCUSSION

These investigations suggest a possible association between factors leading to highly developed local cortical responses and those responsible for epileptogenesis. Certainly cortical cell populations which responded to local repetitive stimulation by exhibiting after-discharge also displayed evoked negative potentials of high voltage in response to single shocks. Conversely, loci resistant to after-discharge showed only a relatively limited capacity to generate these potentials. Moreover, a parallel between responsiveness to single and to repetitive shocks could be extended to include cortical sites of intermediate excitability.

The distribution of high amplitude local responses over the hemisphere found in this study is comparable to that of transcallosal potentials described by Curtis (1940) in the cat and monkey and by Chang (1953) and Peacock (1957) in the cat. The surface negative phase in the latter (callosal), like that of the local cortical response, has been attributed to dendritic depolarization (Chang 1952, 1953; Clare and Bishop 1956). Studies in which surface recording and unit analysis were made simultaneously in the same cortical

area have suggested that induced dendritic depolarization or even spontaneous negative waves in the EEG are associated with increase in frequency of propagated unit responses in the underlying area (Brookhart and Zanchetti 1956; Calma and Arduini 1954; Chang 1951; Whitlock *et al.* 1953). Such observations support the proposal that dendritic depolarization relates to the excitability of the soma-axon (Bishop and Clare 1955; Clare and Bishop 1956; Eccles 1951; Purpura and Grundfest 1956). Therefore, since the evoked responses observed in the present study probably represent dendritic depolarization, it seems possible that the latter may relate to epileptogenesis as well as to normal excitability.

Against this view Jung and Tönnies (1950) have observed that local cortical responses disappear during seizure activity in the same area which they interpreted as indicating normal inhibitory activity (''Bremswellen''). While their experimental observations have been confirmed by others, among them Abdullah and Magoun (1957), we would be more prone to agree with the latter author's interpretation, namely that the disappearance of ''axodendritic'' evoked potentials during seizures may well represent a kind of ''busy-line'' effect due to the involvement of dendritic structures in the generation of seizure potentials. This would be more in line with the data reported in this paper and with Adrian's conclusion that the negative waves of the direct cortical response must represent depolarization, not hyperpolarization, of structures oriented radially to the cortical surface.

Additional support for the proposal that abnormal dendritic depolarization is closely related to seizure production stems from the observation reported here that abnormally large local cortical responses are found in surface loci which are rendered abnormally epileptogenic. A previous report revealed that a contralateral point homotopic to a locus of chronically circumsected motor cortex displayed abnormal spiking and increased tendency for exhibiting afterdischarge upon direct stimulation (Livingston *et al.*). These observations were confirmed in the present report and it was demonstrated, moreover, that such epileptogenic loci homotopic to chronic motor circumsections displayed abnormally large local cortical responses.

Augmented epileptogenesis in the contralateral homotopic area could conceivably result either from distorted callosal or other influences initiated in the circumsected locus or from some focal alteration of function in the homotopic area itself. The fact that the augmented local cortical response elicited in the homotopic site was uninfluenced by elimination of possible inputs from the circumsected zone speaks strongly in favor of the latter possibility. It is a common clinical observation that epileptogenic lesions may elicit focal discharge at the outset but, as time passes, the epileptic process tends to become more generalized. The experiments reported here suggest that such spread of seizure activity is the result of enhanced excitability induced in cell masses remote from a discharging focus but connected with it by intimate association pathways. Such remote loci appear not only to be hypersusceptible to seizures arising in the original focus, but, under certain circumstances, to be capable of eliciting convulsive activity themselves. This phenomenon would appear to relate to experiments reported by Speransky (1943) in which local freezing of the cortex resulted in seizure induction and eventual death through status epilepticus. This course of events was not altered if the focus was resected after the first seizure has occurred but the ensuing decline was prevented if the local removal was made prior to the development of convulsions.

The nature of the process underlying enhanced epileptogenesis in loci remote from an epileptogenic lesion is unknown. Augmented reactiveness in centers distant from experimentally induced injuries in the central nervous system has been ascribed by Teasdall and Stavraky (1953) and by Ward (1953) to sensitivity of denervation. More evidence must accumulate, however, before it can be established that such sensitivity is basically causative in spreading epileptogenesis.

SUMMARY

1. Studies were made on the local cortical potentials evoked in different areas of the monkey brain. These potentials appeared as predominantly surface-negative waves, and consistent patterns in the appearance and amplitude of the responses were exhibited by each area studied. Maximal voltages characterized the "motor area", while minimal deflections were found in the prefrontal and occipital cortex, intermediate values were present in other areas.

2. Correlation was found to exist between the excitability of cortical loci to single-shock stimuli as manifested by local cortical responses and to high-frequency stimulation as indicated by seizure after discharges.

3. When enhanced epileptogenesis was induced in a locus of the motor region by chronically circumsecting an area of cortex in a mirror site on the opposite hemisphere, increased responsiveness to single shocks was observed in the remote cortical locus. This epileptogenic effect was not due to tonic influences from the circumsected area since its excision or procainization or callosal section did not alter the augmented response.

4. The concept of dendritic depolarization as an index of neuronal excitability was discussed in relation to observed variations in the local cortical response. It was proposed that this concept could conceivably be extended to account for differences in seizure susceptibility exhibited by various cortical regions.

RÉSUMÉ

1. Une étude a été faite des potentiels corticaux évoqués en plusieurs aires corticales. Ces potentiels sont surtout des ondes "surface-négatives" et chaque aire corticale étudiée a montré des réponses d'un comportement et d'une amplitude assez constante. Les voltages les plus élevés étaient enregistrés au niveau de l'aire motrice. Le cortex frontal et occipital présentaient les déflections les moins élevées, et des valeurs intermédiaires étaient notées dans les autres aires.

2. Une corrélation a été établie entre l'excitabilité des aires corticales pour des stimuli à choc isolé, mise à l'évidence par la réponse corticale locale et entre l'excitabilité des aires corticales pour des stimuli à haute fréquence, mise en évidence par une post-décharge épileptique.

3. Une épileptogénèse augmentée dans une certaine région de l'aire motrice peut être obtenue dans une préparation chronique en isolant par circoncision, dans l'aire motrice controlatérale et homologue une certaine aire du cortex. Ceci a comme effet d'abaisser le seuil d'excitabilité pour des chocs isolés. Cet effet épileptogène ne semble pas être dû à des influences toniques de l'aire ainsi isolée puisque l'excision ou la procainisation de cette aire ou encore une section du corps calleux ne changeait pas la réponse augmentée.

4. Une discussion est faite de la dépolarisation dendritique comme index de l'excitabilité neuronique en relation avec les variations des réponses corticales locales qu'on a observées. La proposition est faite que cette notion pourrait être employée utilement pour expliquer les différences de la sensibilité convulsive des aires corticales distinctes.

ZUSAMMENFASSUNG

1. Untersuchungen wurden ausgeführt an lokalen, kortikalen Potentialen, welche in verschiedenen Regionen des Affengehirns ausgelöst wurden. Diese Potentiale erschienen als vorwiegend oberflächen-negative Wellen und reproduzierbare Typen von Reizantworten in Bezug auf Auftreten und Amplitude wurden in jeder untersuchten Rindenregion angetroffen. Die höchsten Amplituden wurden in der motorischen Region beobachtet, währenddem minimale Entladungen im frontalen und okzipitalen Kortex angetroffen wurden. Intermediäre Werte wurden in anderen Arealen gemessen.

2. Es wurde festgestellt, dass eine Beziehung besteht zwischen der Erregbarkeit von Rindenarealen in Antwort auf Einzelschocks, welche lokale Rindenreizantworte erzeugen, und derjenigen in Antwort auf hochfrequente Reizung, welche eine epileptische Nachentladung zur Folge hat.

3. Eine erhöhte Krampfbereitschaft konnte erzeugt werden in einem Areal der motorischen Rinde, wenn ein Rindenfeld in spiegel-

bildlicher Lokalisation in der kontralateralen Hemisphäre in einem chronischen Experiment umschnitten wurde. Nach einer solchen Umschneidung wurde eine erhöhte Antwortbereitschaft zu Einzelschocks im entfernten kortikalen Feld beobachtet. Dieser epileptogene Effekt war nicht bedingt durch tonische Einflüsse welche von der umschnittenen Rindenregion ausgingen, da Exzision oder Prokainisierung dieser Region, sowohl als auch Durchscheidung des Balkens die erhöhte Reizbarkeit in der kontralateralen Hemisphere nicht beeinflusste.

4. Die Theorie, dass dendritische Depolarisation ein Index der neuronalen Reizbarkeit darstellt, wird besprochen, wobei Bezug genommen wird auf die beobachteten Veränderungen der lokalen kortikalen Reizantwort. Es wird vorgeschlagen, dass diese Theorie vielleicht ausgedehnt werden könnte, um die unterschiedliche Krampfbereitschaft verschiedener Rindenfelder zu erklären.

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PRINTED IN CANADA

TENDON AFFERENTS IN AUTOGENETIC INHIBITION IN MAN [1,2]

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(Received for publication: June 19, 1958)

When a maximal willed effort is made to contract a muscle isometrically, the recorded electromyogram (referred to here as "maximal voluntary EMG") is distinctly lower if the muscle is held in a lengthened position than if it is held in a shortened position (Ralston, Inman, Feinstein and Libet 1950; Inman, Ralston, Saunders, Feinstein and Wright 1952; Joubert and Gueguen 1956).

The present paper is a report of experiments designed to test the hypothesis that a major factor in producing the lower EMG in the lengthened muscle is the initiation of inhibitory afferent impulses from tendon organs of the stretched muscle. Autogenetic inhibition with stretch was originally proposed by Sherrington (1909) to explain the lengthening reaction of spastic muscles in decerebrate animals. The receptors originating these inhibitory impulses are probably the tendon organs (McCouch, Deering and Stewart 1950; Granit 1950; Hagbarth and Naess 1950; Granit and Ström 1951). In our experiments, the decrease in the maximal voluntary EMG took place under conditions that produce high tensions at the tendinous regions, similar to the conditions that initiate autogenetic inhibition in the animal experiments (Hagbarth and Naess 1950; Granit and Ström 1951; Eldred, Granit and Merton 1953).

The hypothesis stated above was tested by examining the effect of muscle length on the maximal voluntary EMG (*a*) before and after locally anesthetizing the region of the tendon below the border of the muscle belly in normal subjects, and (*b*) in patients with degeneration of afferent fibers from the muscle (tabes dorsalis). Additional data on the range of this effect in normal individuals are also reported.

METHODS

Subjects and leg positions. Subjects were 15 normal males, volunteers from the medical and pharmacy students and the staff members and technicians of the School of Medicine, and 11 male volunteers who were outpatients of the Department of Neurology.[5]

The muscle selected for the study of tendon anesthesia, the anterior tibial muscle (usually of the left leg), among other requirements had to have the major portions of its tendon readily accessible to injections of procaine. The subject either sat up (with back supported) or lay on a flat table. With the tests for the effects of stretch before and after producing anesthesia of the tendon, it was essential that the muscle length at which isometric contractions were performed should be reproducible (see fig. 1). A broad leather belt was strapped tightly around the shoe at the level of the instep to minimize any tendency of the subject to attempt movement of the toes as well as of the whole foot. A metal chain connected this belt to a large L-clamp which was attached to a heavy wooden plank that was itself rigidly attached to the table in a vertical position. When it was desired

[1] A preliminary report of these results has been presented (Libet, Feinstein and Wright 1955).

[2] This investigation was supported in part by contract with the Veterans Administration (VAm-23110).

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[5] We are indebted to Dr. Donald Macrae of the Department of Neurology, School of Medicine, University of California, for help in selecting a number of patients appropriate for this study.

to measure the tension on the foot, a strain-gauge dynamometer (Ralston, Inman, Strait and Shaffrath 1947) was inserted in series with the links of the chain. The subject was instructed to keep his heel in contact at all times with the fixed small wooden block. A small hard pillow, placed under the knee joint to produce a slight flexion of the knee, slackened the gastrocnemius slightly and allowed a greater range of stretch of anterior tibial. A belt which was brought over the thigh and strapped to the table helped in maintaining the fixity of the foot position during contraction. In those experiments in which no tendon anesthesia was being produced, exact reproduction of positions was not critical. The isometric condition for each contraction in these cases was maintained by the operator's simply holding the subject's foot and exerting an opposing force just sufficient to counterbalance the force being developed by the subject.

Generally, three reproducible positions of anterior tibial muscle length were selected for each subject: short (S), with the ankle in the maximally flexed position; long (L), with the ankle passively extended as far as possible without producing pain, although the tendon region was allowed to feel tight and occasionally slightly uncomfortable; and intermediate (I), in which the ankle was slightly extended or in resting position. At a signal, the subject tried to flex his ankle, as much as possible. A continuous recording of the EMG was made of a sustained maximal effort lasting several seconds. It should be emphasized that each contraction was performed isometrically, at a given muscle length, and not during any change in length.

Since the gastrocnemius muscle extends over two joints, the positioning for different lengths is complicated and will be discussed in "Results". To maintain the isometric condition during the contraction of this more powerful muscle (usually of the right leg), the subject pressed the sole of his foot against a properly oriented board, which was clamped to the table frame, and he held his body in a fixed position during the effort.

For study of tendon anesthesia in the anterior tibial muscle, several control runs were made and then about 20 cc. of 2 per cent procaine solution were infiltrated at two or three levels into the tendon, most of it near the lower border of the muscle belly where it joined the tendon. The procaine hydro-

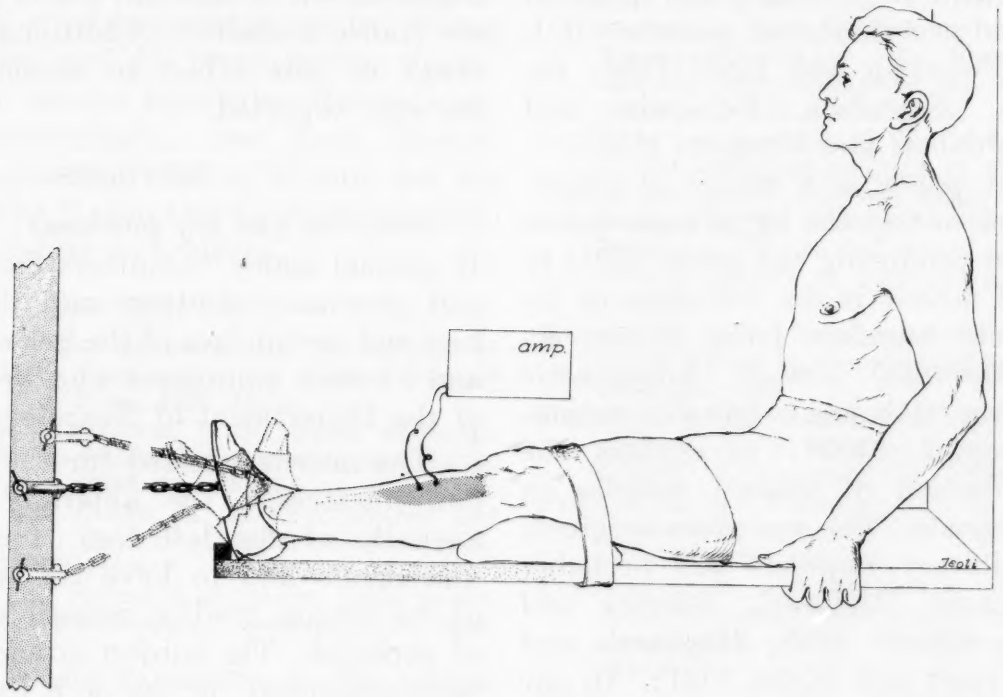

Fig. 1
Diagram to illustrate method of recording, with the anterior tibial muscle active isometrically at reproducible positions, for data reported in table I.

chloride was neutralized to a pH of 7.4 just before use.[1] A few minutes later, series of EMG tests were begun at those muscle lengths used before the injection. Actually, the swelling of the tendon by the injected solution probably resulted in greater passive tensions at these lengths than before the injection. In some subjects, the apparently rapid absorption of this amount of buffered procaine gave mild systemic effects. These symptoms, however, did not usually appear until ten minutes or so after the injection, by which time the tests had been completed with good cooperation from the subject. In several subjects the anesthesia was tested by the absence of any pain following a normally pain-producing injection of about 0.2 cc. of 6 per cent solution of NaCl into the lower part of the tendon.

Electrodes and recording system. Two concave silver discs about 1 cm. in diameter, containing electrode jelly, were fixed onto the lightly sand-rubbed skin about 5 cm. apart over the belly of the anterior tibial muscle. For the gastrocnemius muscle, an electrode was fixed over the approximate center of the bulk of each head of the muscle; this minimized any changes in sampling area with the changes in muscle length. We found that the common method of fixing each electrode onto the skin with collodion could be greatly improved by using a bit of cotton gauze dipped into a thick collodion solution. The electrodes remained firmly fixed throughout repeated movements of the underlying muscle and of the skin during the stretching and slackening procedures.

Whereas shifts in the interelectrode distance with changes in muscle length were inevitable, earlier work had shown that the EMG is relatively unaffected by such differences in location when surface electrodes are used (Inman *et al.* 1952). In addition, our finding described below, that local anesthesia of the tendon abolishes most of the decrease in EMG that is produced by an increase in muscle length, eliminates any argument that this decrease in EMG is due primarily to a change in the electrical sampling of the underlying muscle by the electrodes.

The electrical recording system (see Inman *et al.* 1952) permitted the potentials, after amplification by an RC coupled amplifier, frequency response 20-5000 c/sec., to be recorded directly on a moving photographic paper in a Heiland string-galvanometer oscillograph having a frequency response of 0-500 c/sec. The amplified voltage was also fed in parallel to a circuit which rectified and damped the oscillations, thus producing a "profile" of the EMG amplitude with time, which was recorded simultaneously with the direct EMG. This profile would give undue weighting to relatively isolated peaks that might be separated from other peaks by the damping time period (0.01 sec. time constant). But inspection of the direct EMG potentials indicated that this was not a significant factor in producing the differences in amplitude between different profile EMG's.

RESULTS

Normal Range of EMG Changes with Length

Although the decrease in maximal voluntary EMG with increase in muscle length was reported by Inman *et al.* (1952) for all the muscles they tested, and by Joubert and Gueguen (1956) for muscles of the thigh, there has been no study of the range of the effect among normal subjects for a given muscle. In tables I and II are data on this point for two muscles, the anterior tibial and the gastrocnemius. No attempt was made to achieve an adequate statistical sampling of a given population, the tests being done simply with those subjects who were available. Data are expressed in each instance as a ratio, amplitude of profile EMG for the long (L) position: amplitude of profile EMG for the short (S) position. Absolute amplitudes are unimportant here. The variation in these ratios for the successive tests with a given subject was generally surprisingly small, being on the order of 0.05.

The average EMG amplitude, of the 2.0-sec. period in the recording which contained

[1] Neutralization of procaine hydrochloride to pH 7.4 greatly increases its penetrative activity across connective tissue barriers, reduces the stinging, and obviates any tissue damage that might be produced by the acid in a procaine-hydrochloride solution (Libet and Feinstein, unpublished).

the highest general amplitude that occurred in each test contraction, was measured on the profile EMG record for use in calculating the ratios in the tables. However, when amplitudes were measured for the highest 1.0-sec. or even for the highest 0.2-sec. period in each test, they generally produced ratios very similar to those for the 2.0-sec. periods.

Anterior tibial muscle. An example of the actual recording of the normal EMG at different muscle lengths is shown in figure 2, a and b. A summary of the data is given in table I. (Ratios for several additional subjects had a similar mean value.)

The mean of the L/S ratios for all of the normal subjects under the age of 50 was about 0.5. However, there were large differences in the L/S ratios among the different individuals. One subject showed for the stretched muscle a decrease in amplitude of EMG profile as large as 90 per cent; others, as little as 20 per cent. There was no consistent correlation of the L/S ratio with the age of the subjects. It was our impression that the subjects in whom the muscle and tendon appeared to have greater elasticity or extensibility, as judged by the ease and range of the ankle-joint motions, in general had the highest L/S

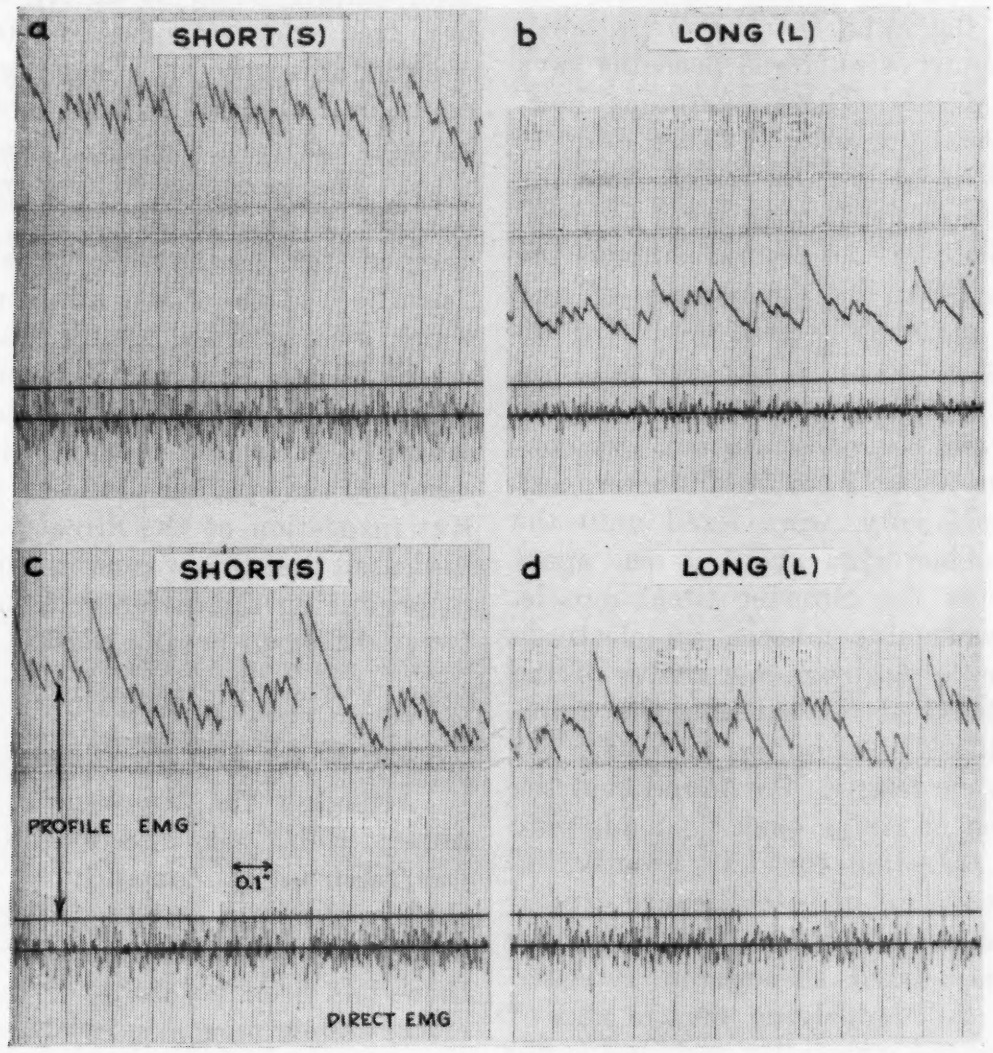

Fig. 2

Effect of tendon anesthesia on the EMG change with length. EMG recording, anterior tibial muscle, isometric during maximal voluntary efforts by subject F.A. In each pair of tracings, the lower is the electromyogram itself (''direct EMG''); the upper is the electrically rectified and damped ''profile'' of the direct EMG. In *a* and *c* the muscle was short (ankle flexed), in *b* and *d* it was long (ankle extended). Figures *a* and *b* were taken before, *c* and *d* after infiltrating 2 per cent neutralized procaine into the tendon.

ratios (*i.e.*, the smallest changes in EMG with stretch). This would be expected if the decreased EMG in the stretched muscle depends upon the production of a certain amount of tension in the stretched tendon.

The EMG at the intermediate length I helps to indicate what part of the range of muscle length is most concerned in the decrease in EMG. The mean I/S ratio of 0.85 in table I shows that there is only a small decrease for this change in length. In addition, there is much less individual variation in the I/S ratio than in the L/S ratio.

Gastrocnemius muscle. Because this muscle extends across two joints, its length may be varied by combinations of both joint positions. The position of maximum muscle length was taken as that with the knee extended and the foot placed with the ankle in the fully flexed position; the intermediate length, with the knee straight but the ankle fully extended; and the short length, with the knee flexed to about 90 degrees and the ankle fully extended. For this muscle, the EMG amplitude was maximal at the intermediate length, instead of the short; therefore, the EMG's at long and short muscle lengths were each related to the EMG at intermediate length (table II).

TABLE I

MEAN RATIOS of *EMG amplitudes* before and after injection with *procaine*. Maximal voluntary contractions of the ANTERIOR TIBIAL muscle at different lengths (L, long; I, intermediate; S, short).

Normal Subject	Age	Mean I/S Ratios			Mean L/S Ratios		
		Control	Procaine	% Change	Control	Procaine	% Change
F.A. (#2)	24	0.49*	0.88*	+ 80	0.11*	0.59*	+ 437
E.W.	34	0.83	0.95	+ 14	0.24	0.75	+ 213
F.A.	24	—	—	—	0.28	0.79	+ 183
H.L.	49	0.97	0.85	— 12	0.37	0.80	+ 116
S.W.	23	0.74	0.74	0	0.43	0.71	+ 65
D.H.	22	0.85	0.73	— 14	0.57	0.67	+ 18
B.L.	39	0.94	0.82	— 13	0.59	0.75	+ 27
L.P.	23	0.82	0.93	+ 13	0.61	0.74	+ 21
J.M.	27	0.90	0.97	+ 8	0.62	0.59	— 5
J.B.	23	0.74	0.73	— 1	0.67	0.70	+ 4
M.K.	22	0.85	0.86	+ 1	0.70	0.81	+ 16
C.W.	22	—	—	—	0.84	0.73	— 13
Mean		0.85	0.84		0.54	0.73	
S.D.		± 0.08	± 0.10		± 0.19	± 0.06	

* Not included in mean (second experiment for this subject).

The decrease in EMG with stretch did not appear to undergo adaptation with time, although this point was not thoroughly investigated. In a few of the experiments, the test for maximal voluntary EMG with the muscle in L position was performed as soon as possible after the muscle had been stretched (within 0.5 min. after beginning the stretch), and, in a separate test, after about 2 min. during which the muscle was maintained in the L position. No significant differences in EMG amplitudes were found between the 0.5-min. and 2-min. test times.

The decrease of EMG amplitude between the intermediate and long positions for the gastrocnemius muscle (L/I ratio, 0.31) was considerably greater than the mean maximum decrease obtainable for the anterior tibial muscle (L/S ratio, 0.54). This was true even for subjects in whom both of these muscles were tested (L.P., J.B., F.A., B.L.).

Gastrocnemius at short length. In the testing of the gastrocnemius muscle, a considerable increase in EMG amplitude occurred be-

tween the shortened length and the intermediate length. This increase can be explained by the facilitation of motoneurones produced by stretch of the muscle spindles; in the range of shorter muscle lengths, these receptors would be more adequately activated by stretch than would the tendon organs that produce autogenetic inhibition (Hagbarth and Naess 1950; Granit and Ström 1951; Eldred *et al.* 1953). No doubt this factor also accounts for the greater EMG amplitude when the gastrocnemius is in the short, isometric condition than when it is in the short, but slackened, state (see *slack-S/isometric-S,* table II).

TABLE II

RATIOS of *EMG amplitudes* for maximal voluntary isometric * contractions of the GASTROCNEMIUS MUSCLE at different lengths (L, long; I, intermediate; S, short).

Normal Subject	Age	L/I	S/I	*Slack-S* / *Isometric-S*
R.G.	22	0.45	0.74	0.12
L.P.	23	0.16	0.16	—
J.B.	23	0.18	0.75	0.26
F.A.	24	0.21	0.64	0.44
O.M.	25	0.48	0.74	0.53
B.L.	39	0.28	0.28	0.67
L.S.	41	0.38	0.56	0.48
H.R.	49	0.32	—	—
	Mean	0.31	0.55	0.42
	S.D.	± 0.12	± 0.24	± 0.20

* Except for recording in the *Slack-S* position.

In the case of the "slack-short" maximal voluntary effort, the operator manually assisted the subject's foot in the direction of the contraction, instead of manually opposing the contraction as in the case of the isometric condition. This *slack-S* contraction of the gastrocnemius muscle often terminated with a cramp of the muscle a few seconds after the start of the test contraction, the cramp being quickly relieved by passively stretching the muscle.

For the anterior tibial muscle, the test in the slack-short condition was only done satisfactorily with five subjects. The average ratio of EMG's, *slack-S/isometric-S,* was close to 1.0 for these subjects. The reason for this high ratio may be that the anterior tibial does not undergo the range of change in tension that the gastrocnemius does; in short position, the anterior tibial is barely relieved of passive tension (even when slackened or unloaded), whereas the gastrocnemius is quite flabby. It is also possible that, when the anterior tibial is put in the short position, the concomitant stretching of the gastrocnemius produces, via the latter's I*b* afferents, facilitation of the motoneurones of the anterior tibial (Laporte and Lloyd 1952; Eccles, Eccles and Lundberg 1957). This facilitation could compensate for any decreased autogenetic spindle facilitation in the anterior tibial in this position.

Effect of Local Anesthesia at the Tendon

After infiltration of the tendinous region below the border of the muscle belly of the anterior tibial with procaine at pH 7.4, ratios of L/S were greater than before the local anesthesia (table I; fig. 2). Indeed, the interesting fact emerges that most subjects, during local anesthesia of the tendon, showed an L/S ratio close to the average value of 0.73 regardless of their normal values. This situation is readily explainable if the differences in normal L/S ratios among the different subjects were due to variations in the effectiveness of the autogenetic inhibition, which was then mostly eliminated by the anesthesia of the tendon organs. The I/S ratios, on the other hand, were little affected by tendon anesthesia (table I), indicating that autogenetic inhibition becomes most effective in the range of length between intermediate and long positions. To judge the change effected by anesthesia of the tendon simply from the mean of the ratios is misleading, the percentage change in the ratio for each individual being more significant. These individual percentage changes may be seen in table I. They provide even more striking evidence for the hypothesis since, as would be predicted by the latter, the subjects with the most autogenetic inhibition (lowest L/S ratio) show the biggest increase in L/S ratio with anesthetization of the tendinous area.

The L/S ratios for successive tests tended to change more following the procaine injection than in the control period. This could be due to variable amounts of time being required for the procaine to diffuse throughout the tendinous tissues and subsequently for the procaine to leave these tissues in different subjects. Even if one uses only the maximum L/S ratio found after the procaine injection in each

case, neither the mean of the ratio (becoming 0.78 instead of 0.73) nor the individual percentage changes are greatly affected. It should also be noted that the absolute EMG amplitudes, not the ratios, were generally lower after the procaine injection than before (*e.g.*, compare fig. 2c with 2a). The local anesthetic agent must have penetrated some motor nerve branches or some muscle fibers in the lower portion of the muscle. But this partial paralysis should not have affected the ratios of EMG's which were obtained at different lengths in the same muscle under the same conditions of anesthesia. In spite of this apparent factor of some direct blockage of muscle response by the procaine, the actual EMG of the stretched muscle was greater after the procaine injection in one half of the subjects and approximately the same or very slightly less in the remaining subjects.

In two subjects an attempt was made, with inconclusive results, to inject the procaine solution into the tendinous regions of the gastrocnemius. It was probably too much to expect that the degree of infiltration used would anesthetize all or most of the tendon organs in the gastrocnemius, which has a large and complicated tendinous structure.

Mechanical tensions, before and during tendon anesthesia. The tensions developed at the foot during the maximal isometric voluntary contraction of the anterior tibial cannot be considered to be a direct measure of the actual tension developed by the anterior tibial muscle, since there may be some unknown contributions to this tension from other muscles cooperating in producing the flexion of the ankle. Also, no particular significance in respect of autogenetic inhibition can be attached to the actual ratio of tensions for L/S or I/S. These measured tensions are affected not only by differences in motor-unit activation (reflected in the changes in EMG amplitudes), but also by the well-known length-tension relationship for the contractile mechanism and by any changes in leverage that may be occurring with altered ankle positions. However, the change in each ratio that occurs after the procaine injection would at least indicate whether these ratios are altered in the direction expected by the hypothesis; the uncontrolled factors that affect the absolute values of these ratios for tensions would tend to be similar before and during tendon anesthesia. The L/S ratios for developed tensions (*i.e.*, total tension minus the passive tension at each length) were in fact larger after the procaine injection than before, the mean of all the individual changes with tendon anesthesia being plus 65 per cent. The mean change in the L/I ratios was plus 26 per cent. For total tensions (including the passive tension), the mean L/I ratio was 1.1 for the controls, and 1.5 during tendon anesthesia (a 36 per cent increase). There was, however, a poor correlation quantitatively between the percentage increase for the tension ratios and that for the EMG ratios for each subject. There was also more variability in the control ratios of the tensions, particularly L/S, than in the ratios of the EMG's.

Tabes Dorsalis Patients

Persons who have lost at least a part of their large muscle afferents should be expected to exhibit less change in EMG amplitude with differing muscle lengths than do normal subjects, according to our hypothesis. Patients with tabes dorsalis would fall into

TABLE III

MEAN RATIOS of *EMG amplitudes* in persons with *tabes dorsalis*. Maximal voluntary isometric contractions of the ANTERIOR TIBIAL MUSCLE in long (L) and short (S) positions.

Subject No.	Age	Mean L/S Ratio
1	53	0.93*
2†	56	0.65* {0.56* (left leg); 0.74* (right leg)}
3	66	0.80*
4	?	0.69*
5	63	0.88*
6	59	0.78
7	69	0.98
8	?	1.00
	Mean	0.84
	S. D.	± 0.13

* Subjects 1 through 5 were asked to look at their feet while exerting the maximal voluntary contraction, in order to check the possibility that lack of proprioceptive information might preclude a proper maximal effort at each length; the other patients were not asked to watch their feet.

† This patient had only mild impairment of postural sensation at the toes (although vibratory sense was moderately depressed at the ankles).

this category; so, perhaps, would the average person over 60 years of age, since considerable degeneration is reported to be present after 60 in the dorsal roots and dorsal columns (Corbin and Gardner 1937; Bailey 1953).

In table III are given the results of tests on patients with tabes dorsalis. The mean of the L/S ratios for maximal voluntary EMG's of the anterior tibial muscle in the tabetic patients is seen to be definitely greater than in the normal subjects, even when the tendons of the latter have been anesthetized. Similar figures were obtained for the two old "normal" men tested (69 years, ratio 0.88; 75 years, ratio, 0.86), but this is obviously too small a sample on which to base any definite conclusions. In addition, a 58-year-old patient who had received a diagnosis of sclerosis of the dorsal columns, and who was unable to detect changes in foot position or vibratory stimulation, also showed a ratio of 0.87. This reduced effect of stretch on the EMG occurred in spite of the presumably greater inelasticity of the tendon in these older subjects.

For the gastrocnemius muscle, adequate tests were done in only two tabetic patients (S.L. and A.D.). In these two, the L/I ratio, 0.65, was distinctly greater than in any of the normal subjects. This is a particularly interesting result, because a satisfactory procainization of the tendinous elements in the gastrocnemius of normal subjects could not be done. The observations in tabetic patients, then, support the inference that the large decrease in EMG at full stretch of this muscle in normal subjects is also due, at least in part, to autogenetic "inhibition" from muscle afferents. The ratios for S/I and *slack-S/isometric-S*, although more variable than those for L/I, average 1.2 and 0.9, respectively, rather than the 0.6 and 0.4 found in normal subjects. This, too, is readily explainable on the basis that the net facilitation, produced by the muscle spindles in this range of stretch in normal subjects, would not occur in tabetics since they lack the afferents that are involved.

DISCUSSION

Tendon anesthesia was found to eliminate much of the decrease in EMG amplitude that normally occurs with stretch of the anterior tibial muscle, showing that this decrease depends upon inhibitory afferent impulses in the region of the tendon. The tabetic (and the few aged) patients further bear out the role of afferents in this effect. The finding by Joubert and Gueguen (1956), that stretching of only the rectus femoris muscle also produced some decrease in the maximal voluntary EMG as recorded in the related muscles, vastus internus and externus, is also explained by such a mechanism.

The retention during tendon anesthesia of some difference in the EMG with different muscle lengths (means of I/S = 0.84, L/S = 0.73) may be explained in several ways. The most obvious explanation would be that not all the tendon organ afferents have been blocked, since some unknown percentage of them may be located in tendinous tissues known to be present elsewhere than at the site of injection (Kolb 1937). Indeed, we were fortunate to have selected for the tendon-anesthesia test a muscle which, by the results of the test, evidently has a significant proportion of its tendon organs located in the vicinity of the main musculotendinous border. The higher L/S ratio in tabetic patients (0.84) than in the normal subjects who have been given tendon anesthesia (0.73) supports this type of explanation. However, some contribution to the decrease in EMG amplitude with stretch in all subjects may come from the greater asynchrony of arrival of muscle impulses at the pickup electrodes (Libet and Feinstein 1951).

The I*b* nerve-fiber group of muscle afferents has been shown to be primarily responsible for autogenetic inhibition, as tested by depression of the monosynaptic reflex in cats (Laporte and Lloyd 1952; Bradley and Eccles 1953). In a more recent study of intracellular inhibitory postsynaptic potentials, Eccles and others (1957) found that the I*b* afferents of extensor muscles produced inhibitory actions much more commonly than did those from flexor muscles, on their respective homonymous motoneurones. This would fit qualitatively with our finding of a much greater inhibitory effect of stretch on

the EMG in the gastrocnemius than in the anterior tibial in man. The variability in I*b* effects seen by Eccles and others (1957) might be related to the large variations in autogenetic inhibition among the different human subjects. The tabetic patients appeared to have lost most or all of their autogenetic inhibition in the anterior tibial and probably in the gastrocnemius. Since it is known that the large muscle afferent fibers are preferentially degenerated in these patients, this would also fit the view that I*b* rather than group III or nociceptive afferents were producing the effect in normal man.

Since stretch does decrease the maximal voluntary EMG in flexor muscles (see also Inman *et al.* 1952; Joubert and Gueguen 1956), although less than in an extensor like the gastrocnemius, it is further unlikely that this effect is due to inhibition at spinal levels from nociceptive afferents (Job 1953). However, the point might be raised that the nociceptive impulses are acting at a cerebral level. The rise in the L/S ratio produced by anesthesia of the tendon might thus be due to a kind of psychological effect, the subject now being more "willing" to exert stronger efforts with the stretched muscle than he was before the procaine injection. But such an explanation seems very improbable (see also Park, Teasdale and Magladery 1951). The position of the foot for the stretched, or long, muscle was set short of that which produced pain, and the subjects were instructed to ignore any other sensations of tightness or mild discomfort when performing their maximal efforts. In one subject (H. L., table I) 10 cc. of procaine was first injected into the tendon at three different levels, all 2 cm. or more below the musculotendinous junction. This first injection produced only a small improvement in the L/S ratio (average 0.37 before, 0.56 after), even though it abolished the sensations of tightness and discomfort in the tendon region. The subsequent injection of 16 cc. of procaine at the musculotendinous border region produced yet another rise in the mean L/S ratio to 0.80.

The *increase* in voluntary EMG reported here with stretch of the gastrocnemius muscle in the *lower* range of its length indicates that, without the aid of some minimal amount of facilitatory impulses arriving from muscle spindles, the descending corticospinal fibers can activate at best only a fraction of the motoneurones. This is in accordance with the early evidence of Mott and Sherrington (1895) on the depression of general motor function in the waking cat following section of the dorsal roots (see also Hyde and Gellhorn 1949). Gellhorn (1948) presumably used conditions of lower muscle tension when he found that stretch facilitated the responses to stimulation of motor cortex.

Consider now some suggestions as to the significance of this autogenetic inhibition for normal motor function in man. Granit (1950) has already pointed out that such an autogenetic governor would increasingly damp the active contraction of a muscle as the tensile stress on its tendon became greater, thus tending to prevent damage, particularly at the junction of the tendon with the muscle belly (McCouch *et al.* 1950). Our preliminary observation that the L/S and L/I ratios, for developed and total tensions on the foot during maximal voluntary contractions, are increased by anesthetizing the tendon area fits this view. Of course, the well-known length-tension relationship for the contractile response itself, also shows a fall in developed tension in the range of greater muscle lengths. This fall would tend to act in the same direction as autogenetic inhibition and thus add with it. Ralston *et al.* (1947) observed such length-tension curves for maximal voluntary efforts in amputees with cineplasty-operated muscles that are freed of leverage complications. However, the actual form of the length-tension curves in at least some of these cineplastic muscles was probably influenced considerably by autogenetic inhibition, these muscles having also exhibited a considerable decrease in EMG amplitude with stretch (see also Ralston 1957).

If the contraction in a muscle "cramp" is associated with the usual motor-unit potentials (Norris, Gasteiger and Chatfield 1955), then the initiation of the cramp (at short muscle lengths) and its abolition (by stretch-

ing the muscle) may be related, respectively, to an absence and a production of autogenetic inhibition.

The role of the autogenetic inhibitory effect in normal, submaximal, short-lasting contractions in man is probably considerably less than in the maximal, sustained efforts that were studied here. However, evidence for the production of autogenetic inhibition during test reflexes in man has been reported by Park and others (1951) and by Buller and Dornhorst (1955). During each walking cycle in man, the contractions of a given muscle take place at approximately intermediate length of the muscle (Inman and Eberhart 1955) and are of brief duration — 0.1-0.2 sec. (Eberhart and Inman 1951; Libet 1953). It is thus unlikely that any strong autogenetic inhibitions are developed during the walking cycle. However, a number of muscles (anterior tibial and certain other flexors) contract at a time in the walking cycle when they are being passively stretched (Eberhart, Inman and Bresler 1954). In such instances, it is possible that tensions on the tendon are great enough to initiate significant degrees of autogenetic inhibition; this inhibition might be a factor in automatically modulating the contraction of that muscle at the appropriate point in the rhythmic walking pattern.

SUMMARY

The range of the changes in the human electromyogram (EMG) with different muscle lengths was investigated for the anterior tibial and gastrocnemius muscles, and the mechanism of the changes was analyzed. In a normal group of men, a maximal voluntary isometric contraction of the anterior tibial when the muscle was in a stretched position gave a recorded EMG amplitude that was on the average 50 per cent below that recorded when the muscle was in a shortened position. For this muscle, the largest decrease of EMG amplitude occurred between the intermediate and long positions. For the gastrocnemius, the EMG amplitude of the stretched muscle was on the average only 31 per cent of that at intermediate length; at short lengths, however, EMG's in this muscle were smaller than those at intermediate length.

The hypothesis that the lower EMG of the stretched muscle is due in part to autogenetic inhibitory afferent impulses from tendon organs was tested by infiltrating with procaine the main tendon region of the anterior tibial. This local anesthesia considerably raised the ratios of the response of the stretched muscle to that of the shorter muscle, for the EMG amplitudes and, less clearly, for tensions produced at the foot. Further supporting evidence was obtained from patients with lesions of the large muscle afferents, mostly those with tabes dorsalis, who showed a much smaller effect of stretch on EMG than did the normal subjects.

The possible role of autogenetic inhibition in regulating some normal motor functions is also discussed.

RÉSUMÉ

Les variations de l'électromyogramme du muscle tibial antérieur et du jambier postérieur pour les longueurs musculaires différentes ont été investiguées, et le mécanisme de ces variations a été analysé. Dans une population normale, une contraction volontaire isométrique maximale du muscle tibial antérieur avec le muscle en étirement présente une amplitude de l'EMG qui en moyenne est 50 pour cent en dessous de la valeur de l'amplitude de l'EMG qu'on obtient quand le muscle est raccourci. Pour ce muscle, le décroissement maximal de l'amplitude de l'EMG se présentait entre la position intermédiaire et la position en étirement. En ce qui concerne le muscle jambier postérieur, l'amplitude électromyographique du muscle en étirement n'était en moyenne que 31 pour cent de la valeur de l'amplitude de l'EMG en position intermédiaire; néanmoins, on enregistrait du muscle en raccourcissement des tracés électromyographiques de plus faible amplitude qu'en position intermédiaire. Nous avons testé l'hypothèse que l'amplitude plus basse de l'EMG du muscle en étirement est due, en partie, à des impulsions autogènes inhibitrices des organes tendineux, en infiltrant avec de la procaine le tendon du muscle tibial

antérieur. Cet anesthésique local augmentait considérablement le rapport de la réponse du muscle en étirement à la réponse du muscle en raccourcissement, en ce qui concerne l'amplitude de l'EMG, et de façon moins claire en ce qui concerne la tension produite au niveau du pied. On a obtenu plus d'évidence pour cette hypothèse en examinant des malades qui présentaient des lésions des nerfs afférents musculaires larges, surtout des malades qui souffraient de tabès. Ces malades présentaient des variations électromyographiques moins importantes quand leurs muscles étaient étirés que ne le faisaient les sujets normaux.

Le rôle possible de l'inhibition autogène dans la régulation de certaines fonctions motrices normales est également discuté.

ZUSAMMENFASSUNG

Die Variationsbreite der elektromyographischen Veränderungen beim Menschen, welche mit verschiedenen Muskellängen auftreten, wurde für den M. tibialis anterior und den M. gastrocnemius untersucht. Der Mechanismus, der diesen Veränderungen zugrunde liegt, wurde analysiert. In einer Gruppe von normalen männlichen Versuchspersonen erzeugte eine maximale, willkürliche, isometrische Kontraktion des M. tibialis anterior im gestreckten Zustand einen Amplitudenwert des Elektromyogramms, welcher durchschnittlich 50 Prozent unter demjenigen lag, welcher in demselben Muskel im verkürzten Zustand gemessen werden konnte. In diesem Muskel ereignete sich die grösste Verminderung der Elektromyogrammamplitude zwischen der mittleren und gestreckten Position. Im Gastrocnemius war die Elektromyogrammamplitude des gestreckten Muskels im Durchschnitt nur ungefähr 31 Prozent des Wertes, der in mittlerer Länge gemessen wurde. Im verkürzten Muskel jedoch war die Elektromyogrammamplitude in diesem Muskel wiederum kleiner als in der mittleren Länge.

Die Hypothese, dass die verminderte Amplitude des Elektromyogramms im gestreckten Muskel teilweise bedingt ist durch autogenetische afferente Hemmimpulse, welche von den Sehnenrezeptoren ausgehen, wurde experimentell untersucht, indem die Hauptsehnengegend des M. tibialis anterior mit Procain infiltriert wurde. Diese Lokalanästhesie verkleinerte den Unterschied zwischen der elektromyographischen Amplitude des gestreckten Muskels und der des verkürzten Muskels in beträchtlichem Masse. Es bestand jedoch eine weniger klare Veränderung der am Fuss direkt gemessenen mechanischen Spannung. Weitere Anzeichen, welche die vorgeschlagene Hypothese unterstützten, wurden bei Patienten mit Läsionen der Nervenbahnen gefunden welche afferente Impulse von den Muskeln zum Zentralnervensystem leiten. Die meisten dieser Patienten litten an Tabes dorsalis. Unter diesen pathologischen Bedingungen übte Streckung des Muskels einen viel kleineren Einfluss auf das Elektromyogramm aus als in normalen Individuen.

Die mögliche Rolle der autogenetischen Hemmung für die Regulation von gewissen normalen, motorischen Funktionen wird ebenfalls besprochen.

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PRINTED IN CANADA

CLINICAL AND LABORATORY NOTES

Edited by R. S. SCHWAB, M.B. and H. FISCHGOLD, M.D.

A VARIETY OF FAMILIAL LIGHT SENSITIVE EPILEPSY

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(Received for publication: June 3, 1958)

In recent years light sensitive epilepsy has provoked sustained interest. In some instances an hereditary factor apparently is involved. Previously, one of us (Daly and Bickford 1951) reported the occurrence of photosensitive epilepsy in middle-aged identical twins whose seizures had been provoked by light since childhood. Davidson and Watson (1956) have recently reviewed the problem and reported studies on 16 families. They have observed that both clinical and electroencephalographic evidence of sensitivity to light existed in a significant number of persons comprising these families. The majority of their patients were subject only to seizures. From their studies, these authors have postulated the existence of a syndrome of hereditary light sensitive epilepsy as a manifestation of "diffusely distributed neuronal affection". Recently we have studied a family in which three members gave evidence of structural disease of the nervous system; sensitivity to light was present only in the affected members. We are reporting this study since it contributes to our understanding of the significance of light sensitive epilepsy.

REPORT OF CASES

The "S" family consisted of the parents and four children. The parents were unrelated; the father was of Rumanian descent; the mother, Irish. The father had diabetes mellitus, as did his father and a brother of his father. No known familial diseases existed in the mother's family. Three of the children suffered from the disease to be described; namely, spastic paraparesis, mental retardation and sensitivity to light.

Case 1. The first child, a 14-year-old boy, had always been retarded in his mental development according to the mother. Her pregnancy had been uneventful; the delivery, spontaneous. The child had sat at 7 months, crawled at 9 months and pulled himself up at 9 months. He first spoke at 3½ to 4 years of age. He had begun to walk at 14 months. From the time of his first steps, his walking seemed awkward. Over the years his gait had improved somewhat; however, at 8 years of age he had injured his right leg and from that time the parents believed his walking had slowly deteriorated.

Examination revealed visual acuity of 20/60 in the right eye and 20/50 in the left eye. The ocular fundi appeared normal. His gait was extremely spastic. The tendon stretch reflexes were hyperactive. Babinski responses were present bilaterally. Sensation was normal.

Results of examination of blood and urine were normal. Roentgenograms of the skull were interpreted as normal. Psychometric testing showed an intelligence quotient of 47, on the Wechsler Intelligence Scale for children.

Electroencephalographic Examination. Recordings made while the patient was lying quietly with his eyes closed revealed an alpha rhythm of 9 c/sec. Frequent paroxysms of rhythmic sinusoidal waves at frequencies of 3 c/sec. were recorded from electrodes over the posterior region of the head. Usually the bursts were bilaterally synchronous, but at times they arose independently from either side (fig. 1). When the patient opened his eyes, the bursts tended to disappear. Waves having a frequency of 4 to 5 c/sec. appeared over more widespread areas of the head; these appeared independently of the slower rhythms. Hyperventilation by the patient did not alter the character of the record.

Photic stimulation was carried out with the use of brief, intense single pulses of light from a gas-filled flash tube. The repetition rate of the flashes was varied in a stepwise fashion between 1 and 30 flashes per sec. For each frequency, the duration of the stimulus was 15 sec. with intervening periods for rest. Stimulation was carried out first with the patient's eyes open and then closed.

Abnormal responses to photic stimulation occurred only when the patient's eyes were open at stimulation frequencies between 15 and 30 flashes per sec. Stimulation for 2 to 5 sec. evoked bursts of generalized high voltage spike-and-wave discharges (fig. 1). The spike component varied in amplitude but usually was greatest in the first complexes of a burst. If stimulation was prolonged, the bursts waxed and waned but tended to increase in duration up to 7 or 8 sec. Frequently the bursts were associated with myoclonic jerkings of the extremities and deviation of the head and eyes to either side. These seizures were too brief to permit detection of any change in consciousness.

Case 2. The second child was a 12-year-old boy. The mother reported that this pregnancy also had been uneventful. So far as the mother knew, the child had seemed normal at birth. He had sat at 8 months,

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crept at 10½ months and stood at 14½ months. He had begun to take steps at 15 months and walked alone at 20 months. He was toilet trained for urine at 2 years, for bowel movements at 4 years. From the first, the mother had noted an abnormal gait which she thought resembled that of the older brother.

Visual acuity was 20/70 right eye and 20/20 left eye. The right eye exhibited a slight convergent strabismus. The appearance of the optic fundi was normal. Examination revealed a spastic weakness of the legs similar to that of his brother. The tendon reflexes were generally increased and Babinski signs were elicited bilaterally.

Results of examination of blood and urine were normal. Roentgenograms were interpreted as normal. The clinical psychologist reported an intelligence quotient of 60.

Electroencephalographic Examination. When the boy lay quietly with his eyes closed an alpha rhythm of 9 c/sec. appeared. Short bursts of rhythmical waves at 2 to 3 c/sec., or isolated waves at an equivalent frequency, were often seen. Usually they were bilaterally synchronous (fig. 2). Discharges at 5 to 7 c/sec. appeared even more frequently. The recording resembled that of the older boy. Hyperventilation by the patient did not produce a change in the record.

The abnormal responses to photic stimulation, as in the older boy, developed only when his eyes were open as the stimulation frequency exceeded 15 flashes per sec. After a few seconds of stimulation, paroxysms

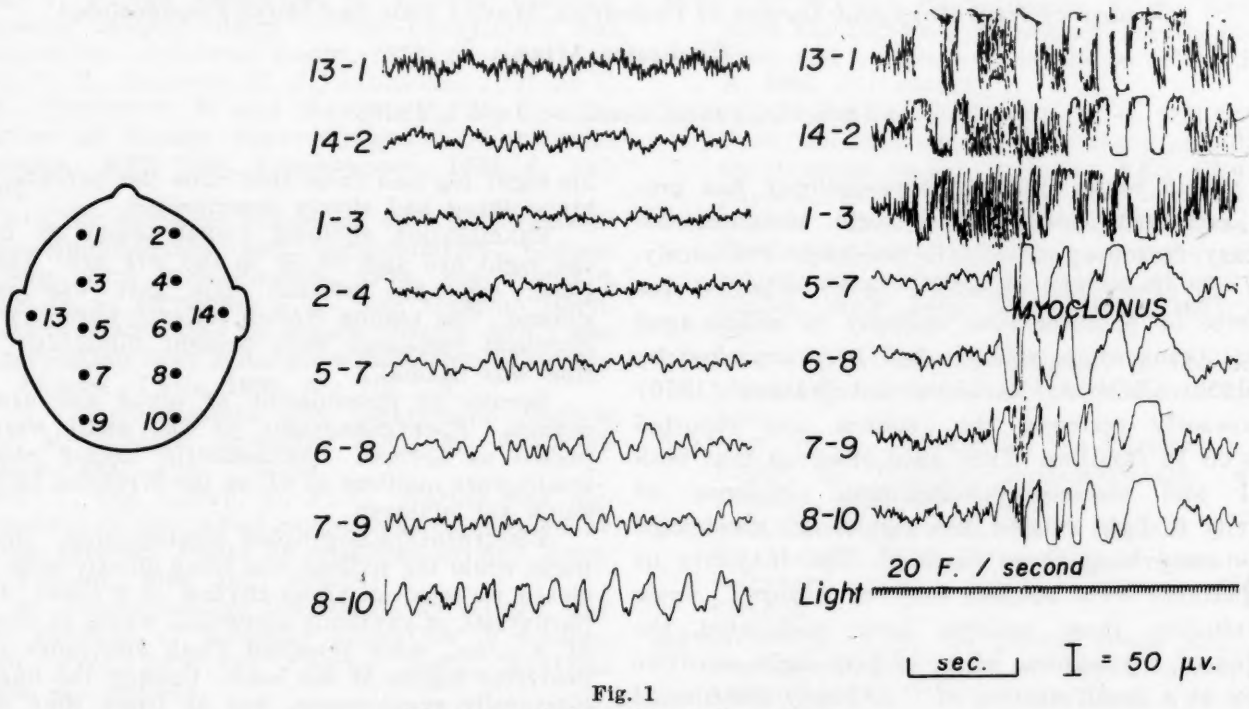

Fig. 1
Electroencephalographic studies, case 1.

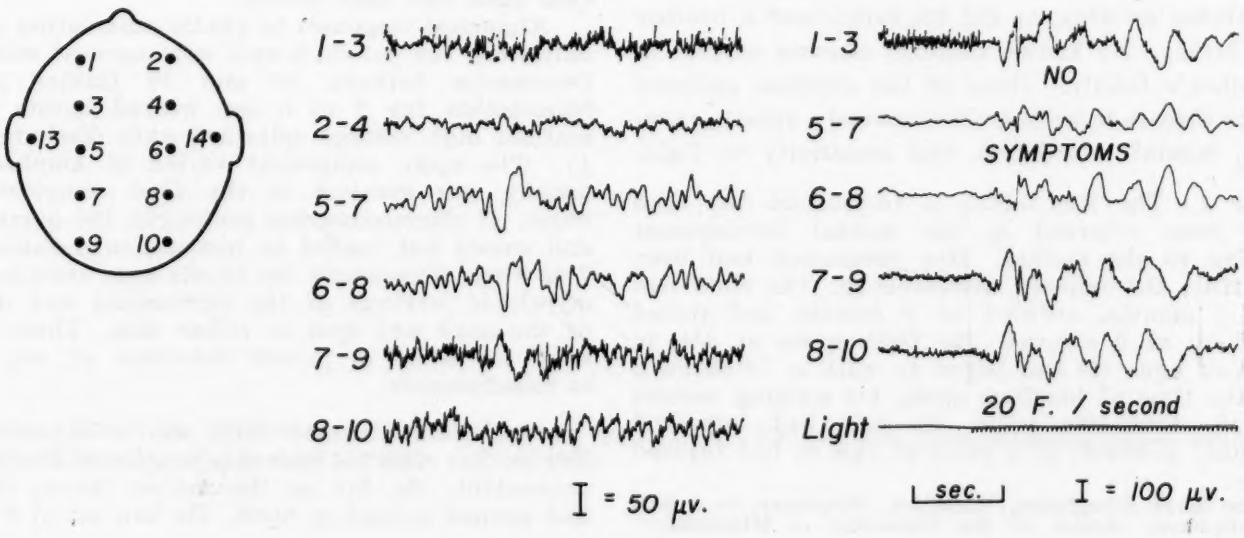

Fig. 2
Electroencephalographic studies, case 2.

of high voltage spike-and-wave discharges developed at a frequency of 3 c/sec. Even with prolonged stimulation the bursts rarely exceeded 2 sec. in duration although they waxed and waned in the same fashion as those of the older boy. No clinical seizures accompanied the abnormal discharges.

Case 3. The third child, an 8-year-old girl, had had a normal birth and development. She had seemed of normal intelligence to the parents and her progress in school had been satisfactory.

The results of physical and neurologic examinations were normal.

Electroencephalographic Examination. The recording made in the resting state revealed an alpha rhythm of 9 c/sec. Occasional low voltage waves having a frequency of 5 to 6 c/sec. were recorded from electrodes in the frontotemporal region; these we regarded as normal for a child of her age (fig. 3). The record was unchanged when the child hyperventilated.

Photic stimulation induced low amplitude driving responses but abnormal discharges did not occur.

Case 4. The fourth child, a 6-year-old girl, had been delivered without untoward incident after a normal gestation. She had sat at the age of 8 months, crept at 10 months and walked at 12 months.

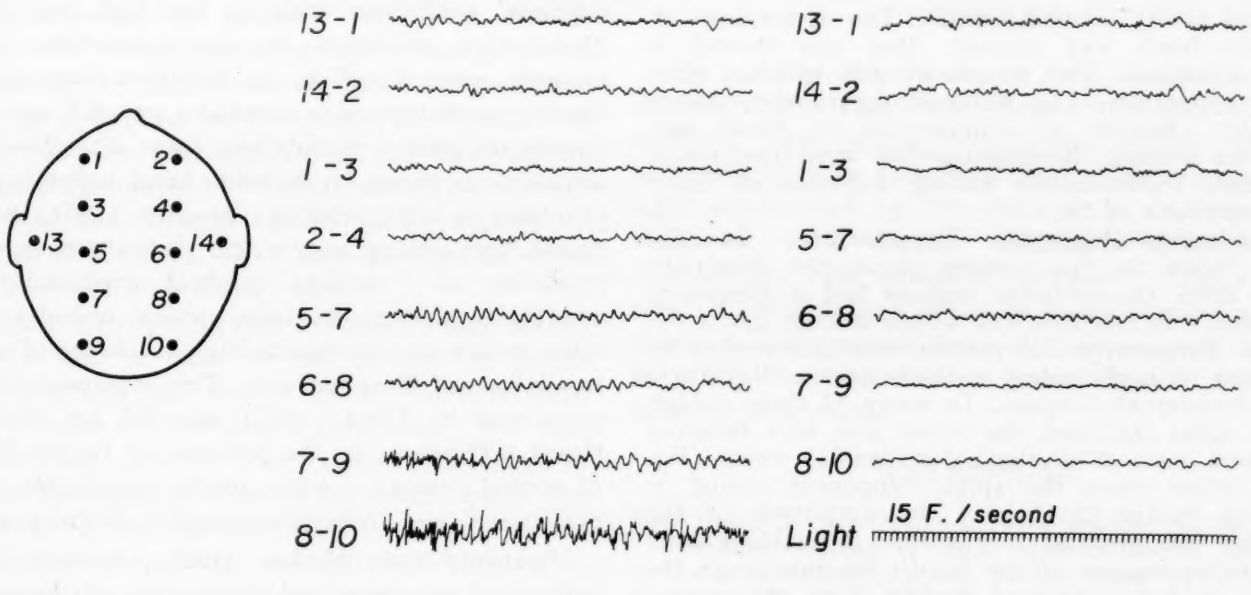

Fig. 3
Electroencephalographic studies, case 3.

She had spoken single words at 18 months of age but had not used sentences until she was 4 years of age. As soon as she had begun to walk, her gait had appeared unsteady, waddling and abnormal. She was hard to train in bladder and bowel function. Her mother had regarded her as somewhat retarded mentally.

At age 13 months several generalized convulsions had occurred in association with a high fever. After this illness her walking had been impaired for a time.

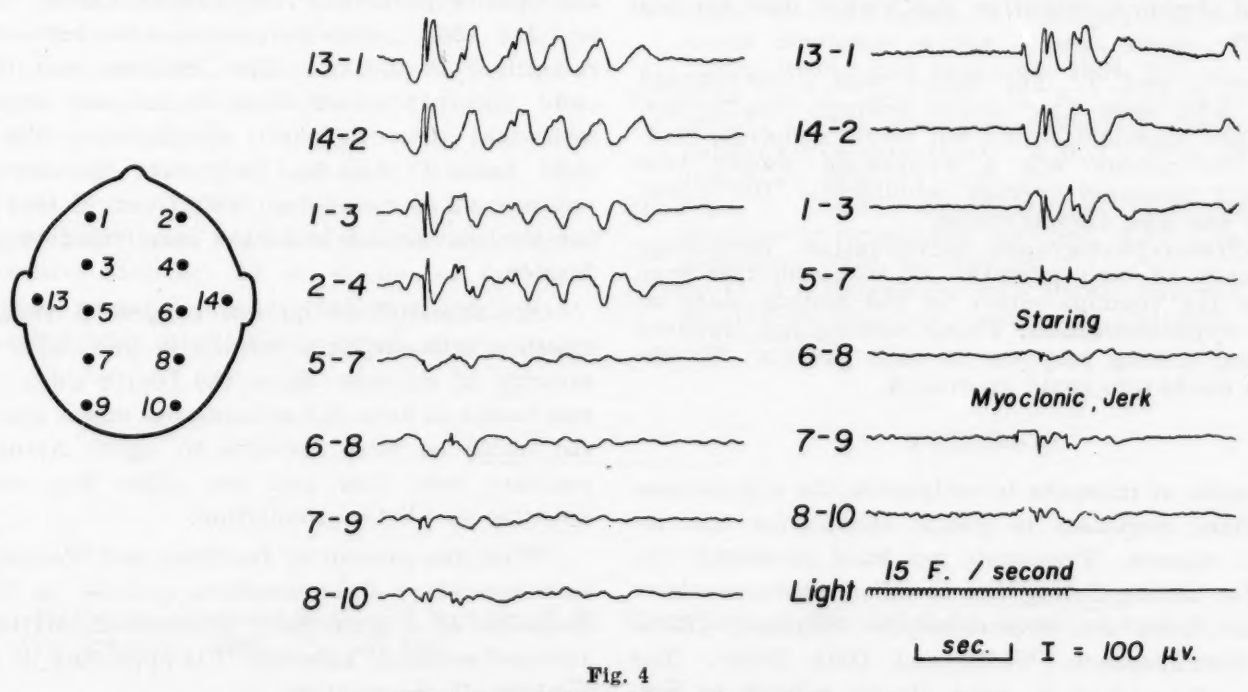

Fig. 4
Electroencephalographic studies, case 4.

At 16 months of age she again had convulsions during a febrile illness. A pneumoencephalogram was made at that time and was interpreted as showing no abnormalities. At 3 years of age she had contracted measles and once more suffered generalized convulsions. At 4 years of age seizures had recurred during a period of fever. Otherwise the parents had never observed any evidence of seizures or myoclonic jerkings.

Visual acuity seemed normal. The appearance of the optic fundi was normal. Her legs showed a spastic weakness. The muscle stretch reflexes were slightly hyperactive and Babinski signs were elicited bilaterally. Results of examination of blood and urine were normal. Roentgenograms were interpreted as normal. Psychometric testing disclosed an intelligence quotient of 86.

Electroencephalographic Examination. In the tracing taken in the resting state, the dominant rhythm from the occipital regions had a frequency of 7 c/sec.; we felt this was within normal limits for her age. Frequently this pattern was interrupted by paroxysms of high voltage spike-and-wave discharges at a frequency of 2 c/sec. In many of these a high voltage spike initiated the burst and was followed by a short train of rhythmical sinusoidal waves (fig. 4); at other times the spike component varied in amplitude during the burst. The amplitude of the complexes was greatest in electrode derivations from the anterior regions of the head. No change in the patient could be observed during these paroxysms. The child would not co-operate in hyperventilation.

Photic stimulation induced only a few abnormal paroxysms in this child. During one of these the patient manifested myoclonus of the extremities and momentary staring (fig. 4). The electroencephalogram then showed spike-and-wave complexes similar to those occurring spontaneously. In contrast to the ease with which photic stimulation evoked abnormal discharges in the patient's brothers, repetitive and prolonged stimulation was often ineffective in this child. However, we believe that the myoclonic seizure was clearly not a fortuitous occurrence and that abnormal responses were induced. We feel that sensitivity to light existed but that the threshold for eliciting abnormal responses was higher than for her brothers.

Cases 5 and 6. The father was a 43-year-old farmer who seemed of above average intelligence. Neurologic examination did not reveal abnormal findings. The mother was a 34-year-old woman who seemingly possessed average intelligence. Her examination was also unremarkable.

Electroencephalographic Examination. Recordings were made of both parents. No abnormalities were seen in the tracings either in the resting state or during hyperventilation. Photic stimulation produced a normal driving response in both parents. No abnormal discharges could be evoked.

COMMENT

In spite of intensive investigation, the significance of deviant responses to photic stimulation has remained obscure. Previously we have presented criteria for distinguishing the so-called photoconvulsive response from the photomyoclonic response (Bickford, Sem-Jacobsen, White and Daly 1952). The former phenomenon is more clearly related to convulsive states. Patients having seizures which can be induced by light can be arbitrarily divided into three classes (Bickford, Daly and Keith 1953). The first class comprises a group of patients in whom seizures result from exposure to flickering light of an intensity and frequency encountered in daily life. In the second class seizures can be induced only under artificial conditions such as the high intensity of illumination produced in the laboratory as, for example, cases 1 and 4. In the third class abnormal electroencephalographic responses are the sole consequence of photic stimulation (case 2). The photomyoclonic response, on the other hand, presents greater problems in interpretation. Shagass (1954) has suggested that among psychiatric patients it is a manifestation of "deviant cerebral excitability", an admittedly ambiguous term, which includes among other events an abnormally high incidence of seizures in relatives of these patients. This conclusion has been questioned by Ulett (1957) who did not find significant differences in the personal or family histories of normal persons in whom photic stimulation induced paroxysmal electroencephalographic discharges.

Davidson and Watson (1956), however, regard both photoconvulsive and photomyoclonic responses as abnormal and have observed these responses from photic stimulation in asymptomatic relatives of patients with light sensitive epilepsy. These authors suggest that light sensitivity itself is a manifestation of an "hereditary predisposition" which may accompany epilepsy or may be present in people without seizures. Our present observations seem to support this concept. The three affected siblings gave evidence of extensive involvement of the nervous system manifested by mental retardation and bilateral defects in the motor system, described under the term, "familial spastic paralysis", or similar names (Schwarz and Liu 1956). However, no seizures had ever been recognized in the two older children, and the first child (case 1) stated that he had not experienced myoclonus prior to photic stimulation. The fourth child (case 4) had had only four episodes of convulsions, all in association with fever, so that even in her the convulsions had been manifested in a minor fashion.

Our observations do not suggest a simple relationship between light sensitivity and occurrence or severity of seizures. Since the fourth child (case 4) was known to have had seizures, one might assume that she would be most sensitive to light. Actually, the contrary was true and the older boy was most sensitive to photic stimulation.

While the concept of Davidson and Watson (1956) that hereditary light sensitive epilepsy is "a manifestation of a genetically determined, diffusely distributed neuronal affection" is appealing, it does not explain all observations.

These authors have commented that none of the patients or their relatives gave evidence of any focal lesion in the nervous system. Yet Herrlin (1954) has reported abnormal responses to photic stimulation in 19 per cent of children with unilateral seizures. We have studied a patient in whom exposure to a rapidly flickering fluorescent lamp consistently produced occipital lobe seizures. We were able to induce a focal electroencephalographic change and a clinical seizure by high frequency photic stimulation. We also have studied one patient with a tumor in the third ventricle who experienced her first seizure during photic stimulation. Validation of the concept of Davidson and Watson (1956) would require investigation of the relatives of such patients in whom there is evidence of a focal lesion.

In some patients, myoclonic movements may accompany petit mal or may be the prelude to major seizures. Penfield and Jasper (1954) have referred to these attacks as "myoclonic petit mal" and suggested that they resulted from epileptic discharge in subcortical systems. Attacks of myoclonic petit mal had occurred in the identical twins to whom we have previously referred (Daly and Bickford 1951). In similar patients, seizures frequently persist for many years in a setting of normal intelligence and without demonstrable signs of diffuse neuronal disease. Thus in a considerable number of patients evidence of widespread neuronal disease is dubious or, in fact, wanting. Lacking such evidence, one is justified in postulating that the process producing light sensitivity may be limited instead to certain subcortical systems and may not depend on widespread neuronal disturbance, particularly at cortical levels (Bickford, Daly and Keith 1953).

Thus, light sensitivity may be a nonspecific phenomenon. In some instances a relatively discrete defect of subcortical systems or, conceivably, even a defect at a cortical level, will permit the appearance of abnormal responses to photic stimulation. In another group sensitivity to light may be the manifestation of widespread neuronal disease. As Davidson and Watson (1956) suggest, this occurrence of light sensitivity need not be associated with signs of a convulsive disorder. If so, studies of patients with diffuse neuronal disease but not subject to seizures, admittedly a relatively small group, may confirm this concept. Thus, heredity may play its role by mechanisms involving biochemical or anatomic disturbances either in specific subcortical systems or in diffuse encephalic neuronal structures. A more intensive investigation of patients with diffuse neuronal disease may affirm or deny such hypotheses.

SUMMARY

In a study of a family of four children and the parents it was found that three of the four children suffered from mental retardation, spastic diplegia and sensitivity to flickering light. The sensitivity to light experienced by the children in this family is compared with similar conditions described as "hereditary light sensitive epilepsy". The hypothesis is offered that while in some instances sensitivity to light results from diffuse neuronal disease, in others it stems from a more discrete defect in subcortical systems.

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PRINTED IN CANADA

EFFECTS OF A PYRIMIDINE ANALOG, 6-AZAURACIL, ON RAT ELECTROENCEPHALOGRAM AND MAZE RUNNING ABILITY

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(Received for publication: June 14, 1958)

6-Azauracil (1,2,4,-triazine-3,5, (2H, 4H) - dione), an analog of the pyrimidine, uracil, has recently been the subject of study as a carcinostatic agent (Hakala, Law and Welch 1956; Sorm, Jakubovic and Slechta 1956; Jaffe, Handschumacher and Welch 1957). During the course of the first clinical trials of this drug (Welch, Finch and Clement 1956; Shnider *et al.* 1957), symptoms of central nervous system toxicity appeared. These effects were studied further by Wells and co-workers (Wells, Ajmone-Marsan, Frei, Tuohy and Shnider 1957) who began dosage of human subjects at 4.5 to 9 mg/kg/day and slowly increased the daily intake of 6-azauracil often to several times this level over varying numbers of days, until toxicity required cessation of administration of the drug. Of 19 patients given the drug, 17 developed both electroencephalographic and neurological changes. The electroencephalographic changes appeared after several days administration, and their magnitude was directly related to the dosage of the drug employed. They consisted of abolition of the fast rhythms; disorganization of the background activity with moderate amplitude, irregular slowing; depression or disappearance of the response to photic stimulation, and appearance of high amplitude delta rhythm. It is notable that these electroencephalographic abnormalities usually appeared in advance of any detectable change in mental status. Eventually, lethargy, somnolence, confusion and semicoma occurred. Other signs of neurological disturbances were unsteady gait, jerking movements of the head, increased deep tendon reflexes and ankle clonus. All changes were reversible upon cessation of the drug.

Elucidation of the means by which 6-azauracil produces central nervous system toxicity is important for the following reasons. First, because any pharmacological agent which produces a severe electroencephalographic abnormality consistent with cerebral dysfunction in the conscious and apparently alert subject is of theoretical interest, especially with reference to the relationship between brain arousal mechanisms and consciousness. Second, because central nervous system toxicity is the immediate limiting factor in the use of 6-azauracil as a carcinostatic agent in man. Adequate investigations of the neuropharmacology of 6-azauracil have been precluded by the fact that no suitable animal other than man has shown comparable central nervous system toxicity. For instance, as much as 2000 mg. of 6-azauracil has been given intravenously to cats without any change in the electroencephalogram (Wells, Ajmone-Marsan, Frei, Tuohy and Shnider 1957). It has been observed however (Welch, Handschumacher and Jaffe 1957 and 1958), that a state of narcosis may be induced within about one hour in laboratory mice and in laboratory rats weighing less than about 200 g. by the intraperitoneal administration of massive doses of 6-azauracil (1000-3000 mg/kg.) as compared with the dosage in man which is required over a period of several days (a total dosage of 25-200 mg/kg.). The purpose of this paper is to show that the white rat is a suitable laboratory animal upon which to carry out certain basic investigations of the action of 6-azauracil on the central nervous system.

MATERIALS AND METHODS

The following observations were made upon 20 male white rats of the Charles River strain, which varied between 60 and 100 g. in weight. Fourteen of these were fitted with permanent cortical electrodes by a modification of the method of Hoagland (Hoagland 1941). The electrodes were fashioned from steel phonograph needles, carefully placed through the exposed skull with a hand chuck and fixed in place with dental cement. Four electrodes were positioned in each animal, 2 in the vicinity of the coronal and 2 near the parietal-interparietal sutures, the members of each pair being equidistant from the midline. On routine gross post-mortem examination the electrode tip generally rested upon, or slightly depressed the dura mater. The cortical gray matter was penetrated on a few occasions. During an experiment the animal remained unanesthetized but was restrained in a rat holder, and bound with Elastoplast in such a manner that only the head was free. Recordings were obtained on a standard 8 channel Grass electroencephalograph, Model III-D. All recordings were bipolar. 6-Azauracil, with melting point of 272°C. and without detectable impurities, was dissolved in distilled water, 20 mg/ml., adjusted to pH 7 (the pKa is approximately 7) with 1 N NaOH and stored at 55°C. Control solutions were prepared: one of uracil, 20 mg./ml.,

and the other of N/11 solution of NaCl (0.53 per cent), which in respect to sodium, is approximately equimolar with the azauracil solution.

RESULTS

The basic electroencephalographic pattern of the awake, but restrained, rat consists, by this method, of 60-160μV., 30-50 c/sec. fast activity superimposed upon 140-250μV., 4-7 c/sec. irregular waves in the anterior to posterior leads, often with bilateral synchronization. The anterior and posterior side to side recordings are somewhat lower in voltage with considerably less slow activity and more regular 30-50 c/sec. activity (fig. 1A). Bursts or stretches of 150-500μV., 10-12 c/sec. irregular sharp waves are inconstantly present (fig. 2B). This pattern may be

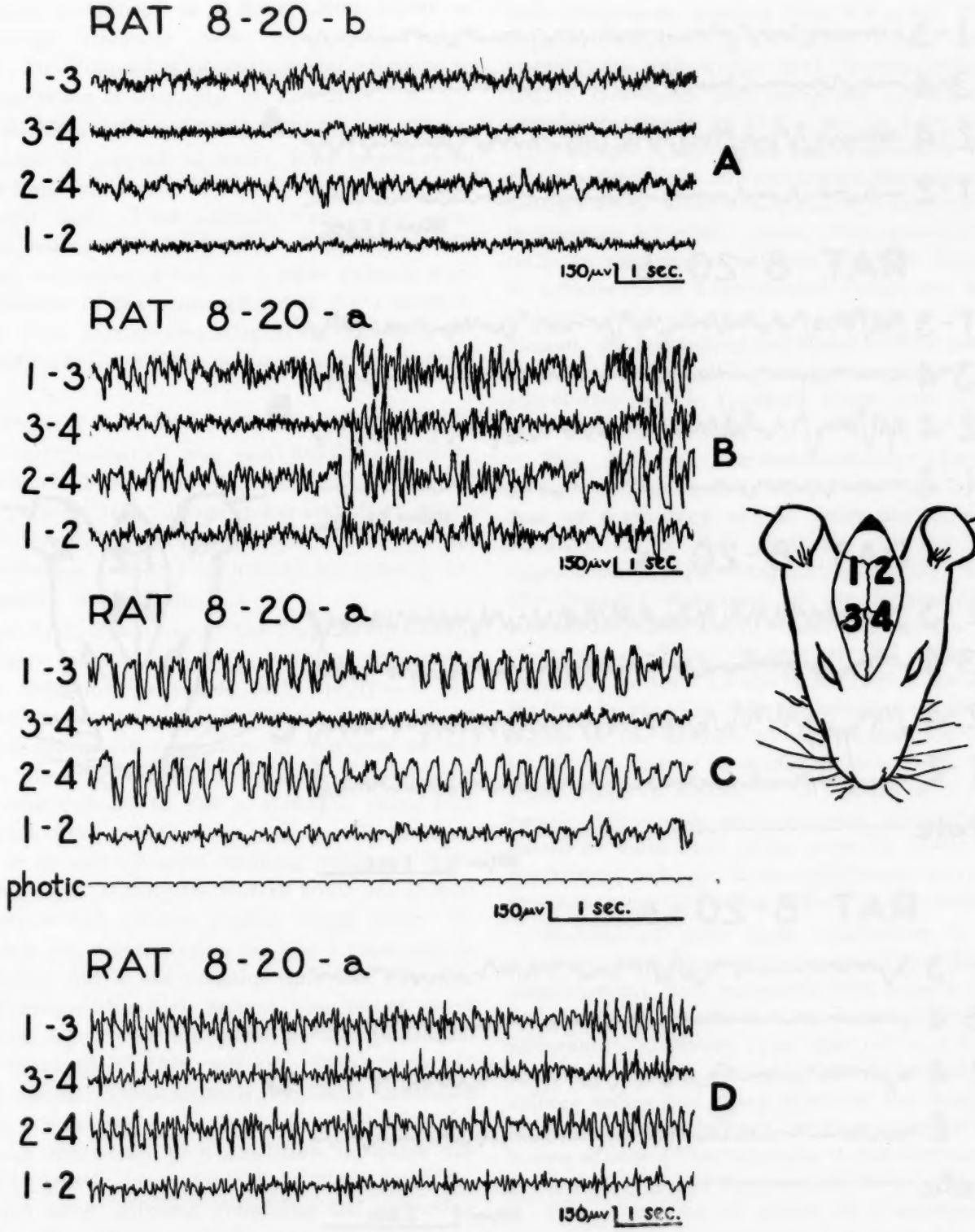

Fig. 1

Normal and control observations.

A. Predominant pattern of the electroencephalogram of the unanesthetized white rat.
B. Electroencephalogram of unanesthetized rat: "dozing".
C. Response to photic stimulation at 6 c/sec. Note induced spike and wave pattern.
D. Fast wave and spike activity produced by pentobarbital, 30 mg./kg.

reverted to the previously described one by strong sensory stimuli. For this reason and because the configuration of the waves is similar to that observed in light sleep in man and in other animals, we believe it appears as the animal dozes. Photic stimulation at 6-10 c/sec. may evoke varying degrees of "driving", the usual response being controlled activity at the driving frequency. In some instances synchronous spike and wave patterns have been observed (fig. 1 C).

Azauracil Effect: After a single intraperitoneal injection of 6-azauracil, 1000 mg/kg., the following

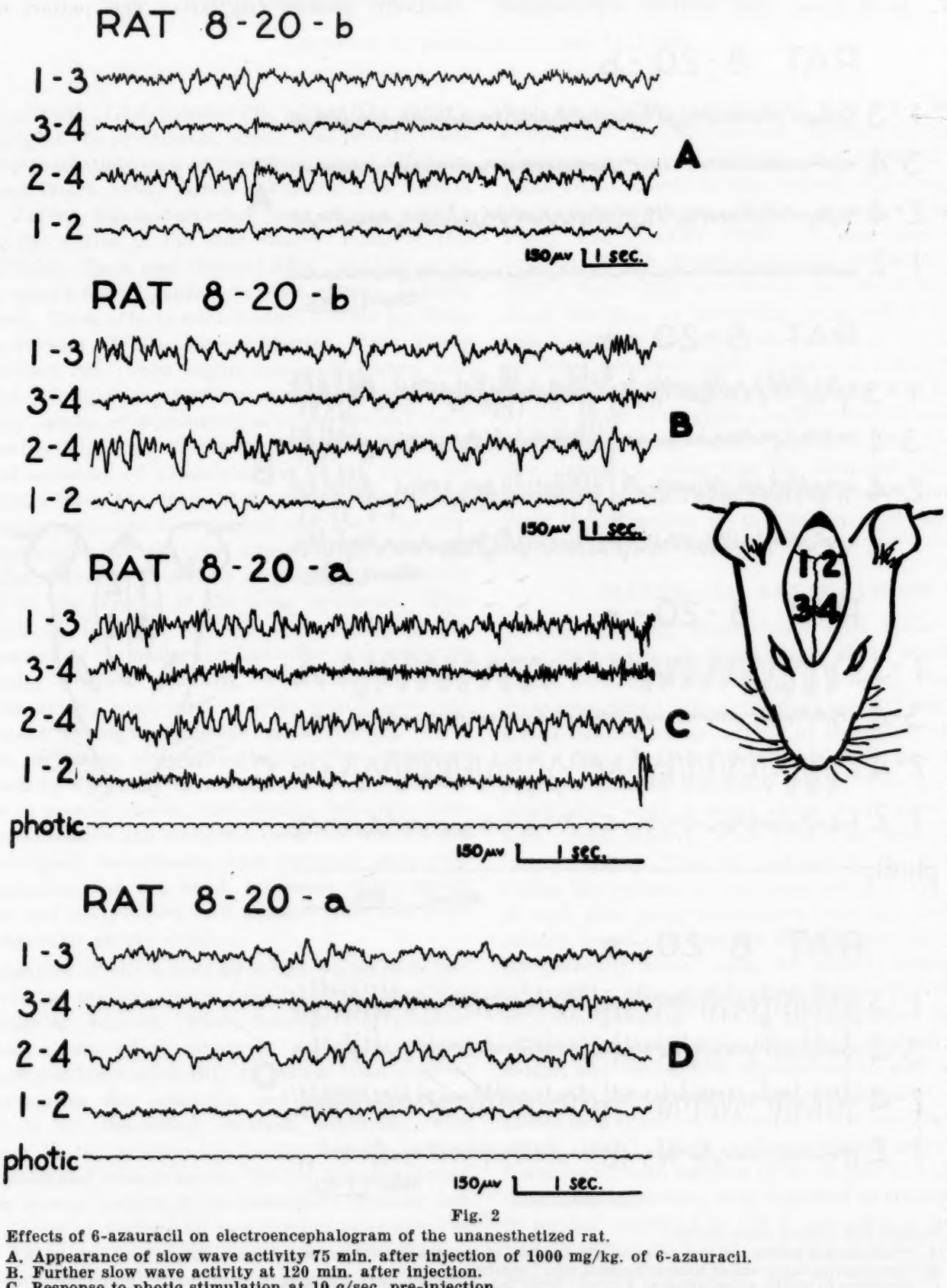

Fig. 2

Effects of 6-azauracil on electroencephalogram of the unanesthetized rat.

A. Appearance of slow wave activity 75 min. after injection of 1000 mg/kg. of 6-azauracil.
B. Further slow wave activity at 120 min. after injection.
C. Response to photic stimulation at 10 c/sec. pre-injection.
D. Absence of response to photic stimulation 120 min. after injection of 1000 mg/kg. of 6-azauracil.

changes in the electroencephalogram may be noted. Within 50-75 min. a noticeable reduction of the amount of 30-50 c/sec. fast activity appears (fig. 2A) which reaches a maximum between 2 and 3 hours after injection of the drug and then gradually returns to the preinjection state, usually within about 6 hours; 10-12 c/sec. high voltage spiking, as described above, often follows the initial slowing and is usually most prominent at 4 hours after injection. High voltage irregular slow waves may occur (fig. 2B), but depression of the cortical response to photic stimulation is seen (fig. 2C and 2D).

Controls: Since the maximum solubility of 6-azauracil is about 20 mg/ml. of water, it is necessary to deliver 3-5-ml. of water intraperitoneally with the experimental dose. Four animals were given comparable injections of 3-5 ml. of a solution of uracil, 20 mg/ml., and these as well as 2 other animals were given injections of the same volume of N/11 solution of NaCl. The electroencephalographic changes described for 6-azauracil were not seen in these control animals.

The effect of a barbiturate, pentobarbital, on the rat electroencephalogram was established as another special control observation. A dosage of 30 mg/kg. produced periodic high voltage spikes and sharp waves (fig. 1D), correlated with somnolence in the animal. These discharges were not influenced by sensory, including photic, stimulation.

T-maze Test: Since one of the features of 6-azauracil toxicity in the human is initially apparently unaltered behavior associated with profound disruption of the electrical activity of the brain, it was decided to obtain some measure of patterns of behavior in the rat. For this purpose, 6 additional animals were trained to run a standard three foot T-maze with food pellets as a reward. The animals received 5, 10 and 10 more training trials on three consecutive days. During the last 10 trials one animal made 2 errors and another made a single error. No animal made any errors during the last 5 trials and in every instance but 2, the running time was less than 3 sec. Subsequently, each animal was tested every 6 min. from 30 to 150 min. after an intraperitoneal dose of 6-azauracil, 1000 mg/kg. There were 15 trials per animal. These animals invariably developed an ataxia which appeared about 60 min. after injection and progressed to a condition in which the animal was grossly incoordinated, hurtling down the alley of the maze, slipping, stumbling and careening off both walls. These animals, however, made no false turns or retracings in a total of 90 trials. Despite the severe motor affliction, no deficit in speed was apparent and the average running time was maintained at about 3 sec.

COMMENTS

There have been a number of investigations concerning the electrical activity of the brain of the white rat. Yoshii and Tsukiyama (1951), using cortical electrodes, cite the basic electroencephalographic frequency as about 6-12 c/sec. with superimposed fast activity. Other authors, although not furnishing a textual description, provide records which show the basic frequencies ranging from 4-8 c/sec. with superimposed fast activity (Lindsley, Finger and Henry 1942; Cahen and Wikler 1944; Girden 1948; Caspers 1953). Overholser and his group (1950) found an average frequency of 30.8 c/sec. in 4 to 8 week old rats. Bergen (1951) also has emphasized the faster frequencies in the rat electroencephalogram. In the present study 30-50 c/sec. activity was found superimposed on 4-7 c/sec. waves. This spectrum is essentially in agreement with the previous investigations if differences in experimental design are taken into account. There is usually a response to photic stimulation. An interesting incidental finding concerns the appearance of a spike and wave response to photic stimulation which appeared from time to time in certain of the animals.

The following electroencephalographic changes occur following acute administration of a single large dose of 6-azauracil to the unanesthetized rat: (1) abolition of the fast rhythms; (2) the inconstant appearance of high voltage, irregular slow waves, and (3) frequent depression of the response to photic stimulation, most clearly demonstrated at a frequency of 10 c/sec. These changes parallel those described in human subjects (Wells *et al.* 1957). An additional finding is that of the appearance of gross motor ataxia in the absence of any diminution of ability to run the course of a simple maze with respect to either speed or accuracy. No conclusion is warranted except that simple maze running ability is not impaired by 6-azauracil given under the above described conditions; however, these experiments serve to focus attention upon the motor effects of the drug.

Because of some basic similarities in chemical structure, 6-azauracil and a representative barbiturate, pentobarbital, were compared with respect to electroencephalographic effects. The barbiturate effect was remarkably different from that of 6-azauracil and was characterized mainly by the appearance of high voltage spikes and sharp waves at the dosage administered. These findings are characteristic of certain known effects of barbiturates on the electroencephalogram (Greville and Heppenstall 1950).

The mechanism of action of 6-azauracil in producing central nervous system toxicity has not been determined. Recent investigations suggest that the brain may have an exogenous requirement for ribose — containing pyrimidine derivatives. Thus, uridine and cytidine were necessary for the maintenance of

metabolism and function in the perfused cat brain (Geiger and Yamasaki 1956). The intraventricular injection in rats, of the 5-hydroxy and 5-amino derivatives of uridine, has produced somnolence, clonic convulsions, and spike-dome and spike discharges in the electroencephalogram (Geiger 1958). Also, the intracisternal injection, in cats, of a nucleic acid precursor analog, 5-fluoro-orotic acid (5-fluorouracil-6-carboxylic acid), has induced signs of cerebellar and brainstem disturbances and histological lesions in the cerebellum (Koenig 1958). Many asymmetrical (1, 2, 4.) triazine derivatives have been found to produce an ascending paralysis, accompanied by depression of multisynaptic reflexes and either anti-convulsive or convulsive action depending on the animal species (Mantegezza, Tommasini, Fusco and Rossi 1953).

At present, the anatomic site of the action of 6-azauracil, whether cortical, upper brainstem or diffuse, remains speculative. Further studies are in progress.

SUMMARY

A single intraperitoneal injection of the pyrimidine analog 6-azauracil has been shown to produce abnormalities in the electroencephalogram of the white rat which are similar to changes observed in man. This is the first demonstration of such experimentally induced electroencephalographic changes in any laboratory animal. Paralleling these effects is a profound ataxia which fails to alter the speed and accuracy with which the animal traverses a simple T-maze. These findings are regarded as preliminary to a further study of the mode of action of 6-azauracil and similar agents on the central nervous system.

The authors are indebted to Dr. Arnold D. Welch, Professor of Pharmacology, for his support and encouragement. The 6-azauracil was supplied by the Squibb Institute for Medical Research, through the courtesy of Dr. Welch.

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PRINTED IN CANADA

PETIT MAL EPILEPSY AND CORTICAL EPILEPTOGENIC FOCI

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(Received for publication: September 22, 1956)
(Revised manuscript received: August 13, 1958)

INTRODUCTION

It has long been recognized that attention to the minor epileptic seizures is most likely to indicate the site of an epileptogenic lesion, while the major attacks seldom give such information, apart from a careful observation of their start. If the minor turns consist of only a lapse of consciousness it is strong presumptive evidence that the patient is suffering from petit mal. This diagnosis will be confirmed by the occurrence in the patient's electroencephalogram of generalized symmetrical spike and wave activity at a frequency of 3 c/sec. If the frequency is slower than this it is most likely that the epilepsy is acquired and the manifestation of a diffuse cerebral disease, unless these abnormal waves show well marked focal features. However, circumscribed lesions on the medial surface of the hemispheres may give rise to generalized spike and wave activity, although this is frequently asymmetrical, irregular in its form and most commonly of a frequency varying between 2 and 2 and a half cycles per sec. (Tükel and Jasper 1954). In explanation of these generalized abnormalities arising from focal cortical lesions it seems reasonable to suppose that the epileptic discharge originating in the parasagittal areas fires into a centrally placed region in the diencephalon from whence it is relayed back to the cortex on both sides (Penfield and Jasper 1947).

Apart from its atypical form, the possibility that such a generalized discharge is of cortical origin may be suggested by the description of the accompanying minor attacks. These may consist of other features than just a lapse of consciousness. For instance in Tükel and Jasper's (1954) analysis of epileptic fits arising in the parasagittal areas the minor seizures consisted of such varied symptoms as palpitations, turning of the head and eyes, vocalisation, forced thinking and clonic movements and sensations in the legs.

However, Howell (1955) in a review of unusual centrencephalic seizure patterns has shown that the classical 3 per sec. spike and wave activity may be associated with minor attacks of considerable variability. Examples included clonic twitching of a limb, brief episodes of giddiness, a sense of impending death, well-formed visual hallucinations, and autonomic phenomena such as progressive slowing of the heart, arrest of respiration and drenching perspiration. Seizures of these unusual kinds could only be accepted as of central origin after the possibility of a cortical epileptogenic focus had been most carefully excluded.

When patients give a history of attacks which at times show various positive features in addition to impairment of consciousness the possibility that they have two entirely separate epileptogenic foci must also be considered. These foci might be due to two quite separate lesions or they might be connected in a way suggested by Howell (1955). In order to try and explain the occurrence of the unusual types of seizures that he found were associated with three per second spike and wave activity he discussed the possibility of an asymmetrical and restricted spread of the epileptic discharge within the central areas of the brain, followed by its projection to a small area of the cortex in one hemisphere. When the discharge reached the cortex it might lead to an attack mimicking a focal cortical seizure. The occurrence of two separate but possibly related epileptogenic foci in a patient with several types of attacks is suggested by the following case record.

CASE REPORT

S. M., aged 20, was admitted to St. Mary's Hospital, London, under the care of Dr. Harold Edwards. He stated that at the age of twelve he fell and injured his head. He was unconscious for about six hours. After this accident his character changed. He began to do badly at school and became irritable, morose and troublesome. At about the age of fourteen he began to suffer from attacks. These might occur several times a day and consisted of a feeling that "time had elapsed", and if someone was talking to him he would not know what had been said. After a while he began to fall in these attacks and they were occasionally associated with a feeling as if his body was rotating in an anticlockwise direction.

In the past year or two he had also started to suffer from major convulsions. These would be preceeded by a wandering of attention, a feeling of giddiness and sickness and a turning of his head in a jerky fashion to one side, probably to the left.

Since about the age of sixteen the patient had, from time to time, been aware of a feeling that he knew exactly what was going to happen. This might occur several times a day and last for a few minutes on end, but did not appear to bear any relationship to the other attacks. He also suffered from other symptoms which appeared to be schizoid rather than epileptic in nature. He realized that in the back-

ground of his mind there was a more or less continuous mutter of voices. Once he tried to concentrate very hard on what was being said when the noise became very loud and he lost consciousness. He tended to become depressed and tense but his general health had remained good.

No abnormal physical signs of significance were ever elicited on examination. The X ray of the skull showed no radiological abnormalities and the only significant change in the first electroencephalogram was a slight excess of low voltage theta activity in the front-temporal regions. A sleep record was normal. However, during another tracing taken while the patient was awake two episodes of fairly regular and generalized 3/sec. spike and wave activity occurred. In further records occasional generalized complexes appeared. They consisted of several moderate voltage slow waves within the theta range irregularly associated with spikes and lasted from 1 to 2 sec. at a time. There was a finding of particular interest in one of these electroencephalograms. Fifty sec. after the end of overbreathing there was an episode of generalized symmetrical spike and wave activity. The slow waves were associated with multiple spikes to begin with, but the spikes soon became single and less marked. The slow waves were initially at a frequency of 3 c/sec. but slowed to 2 and a half c/sec. On two occasions during this apparently typical outburst of spike and wave activity isolated high voltage spikes showing phase reversal in the left fronto-temporal region appeared (fig. 1). This finding seemed to indicate that there were two epileptogenic foci present.

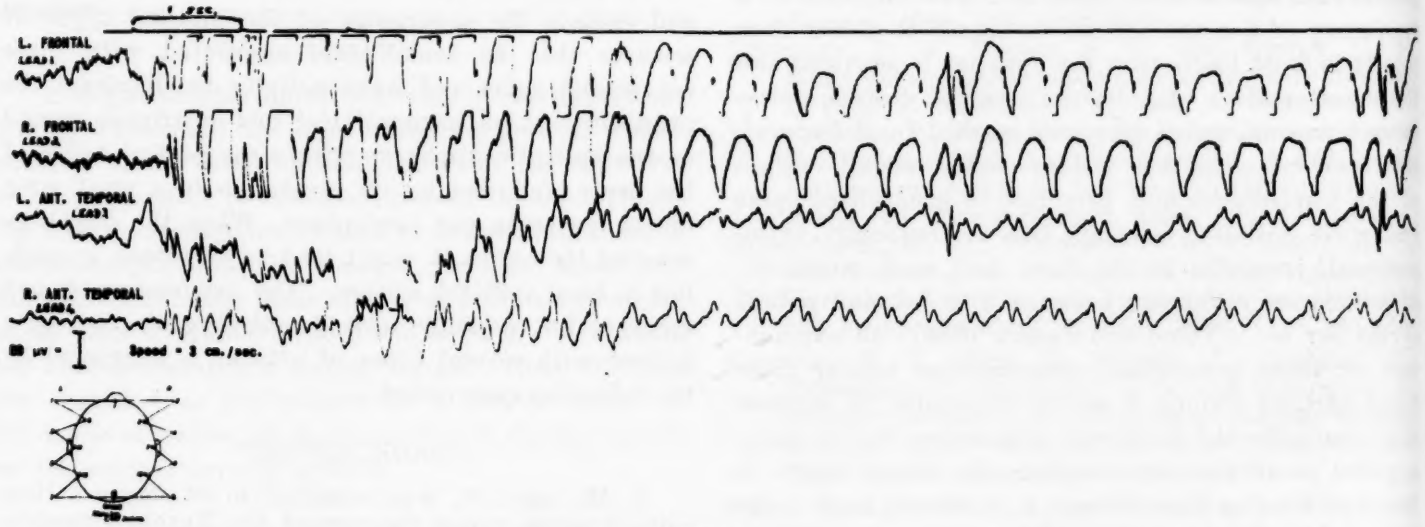

Fig. 1

Electroencephalogram showing anterior temporal spikes occurring during an outburst of generalized spike and wave complexes. (Amplifier blocking unavoidable as the seizure began too suddenly for the necessary adjustments to be made.)

Further investigations were not considered justifiable and the patient was discharged on treatment with phenobarbitone and troxidone. The major and minor attacks were well controlled, but the ''déjà vu'' phenomena continued to occur at frequent intervals.

DISCUSSION

This patient may have been suffering from the effects of two separate epileptogenic lesions or the spiking activity in the anterior temporal region may have been secondary to the diencephalic discharge. Clinically there were two types of minor attacks; lapses of consciousness suggestive of petit mal and ''déjà vu'' sensations suggestive of temporal lobe epilepsy, and they did not appear to bear any relationship to each other. None of the patients' attacks started until after a head injury which raises the possibility that his epilepsy in all its forms was of traumatic origin. It is generally supposed that petit mal is never acquired but in patients suffering from this type of epilepsy it is not uncommon to elicit a past history of trauma or of an illness suggestive of ''encephalitis''. Jasper and Kershman (1941) reported that in 21 per cent of such patients there was a previous history of cerebral trauma.

Jasper (1951), Ajmone-Marsan (1950) and their colleagues found that in animals epileptiform after-discharge could be set up in the tips of the temporal lobes by electrical stimulation of specific thalamic areas. These subcortical connections might explain local electroencephalographic abnormalities in the temporal lobes which appear in the absence of any evidence of a cortical lesion. Lennox and Robinson (1951) postulate that the anterior and mid-line thalamic nuclei, anterior cingulate gyrus and cerebellum belong to a closely integrated system, the discharge from which is responsible for petit mal seizures, and also that on anatomical, functional and electroencephalographic evidence the hippocampal formation and the entrorhinal areas afferent to it should be included within it. This would certainly tend to link up seizures originated within the diencephalon, with those arising from cortical foci in the parasagittal areas and the temporal lobes.

This case report may, therefore, support the contention that epileptic fits do not develop in cortical

or subcortical regions but in the sectors consisting of the two closely interconnected in both directions (Gastaut 1954). It is suggested that this patient developed an epileptogenic lesion in the diencephalon, possibly as a result of his head injury, and that this lesion, although usually giving rise to "petit mal", sometimes caused a discharge to spread to a localised area of the temporal cortex, resulting in "déjà vu" sensations.

SUMMARY

Unusual types of seizure patterns that may be associated with three per second spike and wave activity in the electroencephalogram are reviewed.

A case record is given of a patient who suffered from various types of epilepsy and whose electroencephalograms showed episodes of generalized spike and wave activity, and on one occasion simultaneous epileptic discharges from the diencephalon and the left anterior temporal region.

It is concluded that there is evidence that epileptic discharges may radiate in a system of neurones connecting the parasagittal regions of the cortex, the temporal lobes and the diencephalon; this latter part being able to recruit wide areas of the cortex in a generalized discharge of a specific type.

I wish to thank Dr. Harold Edwards for permission to publish the case record of a patient admitted to hospital under his care.

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PRINTED IN CANADA

ELECTROENCEPHALOGRAPHIC RECORDING IN SIMULATED COMBAT FLIGHT IN A JET FIGHTER PLANE [1, 2]

The Pilot's Level of Consciousness

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(Received for publication: April 1, 1958)

The hostile environment to which a jet fighter pilot is exposed has been pointed out by many authors as a reason for major aircraft accidents. The effects of vertigo/disorientation, G-forces, hypoxia (acute and chronic), fatigue, decompression (slow and rapid), and hyperventilation have been extensively studied in aero-medical laboratories with elaborate equipment.

During 1956, according to Colonel Moseley and Captain Stembridge, 48 per cent of the aircraft accidents were due to pilot errors and 14 per cent were due to "cause undetermined". Thus, the possibility exists that in 62 per cent of the aircraft accidents in that year, an inadequate response on the part of the pilot might have been responsible for the fatal result.

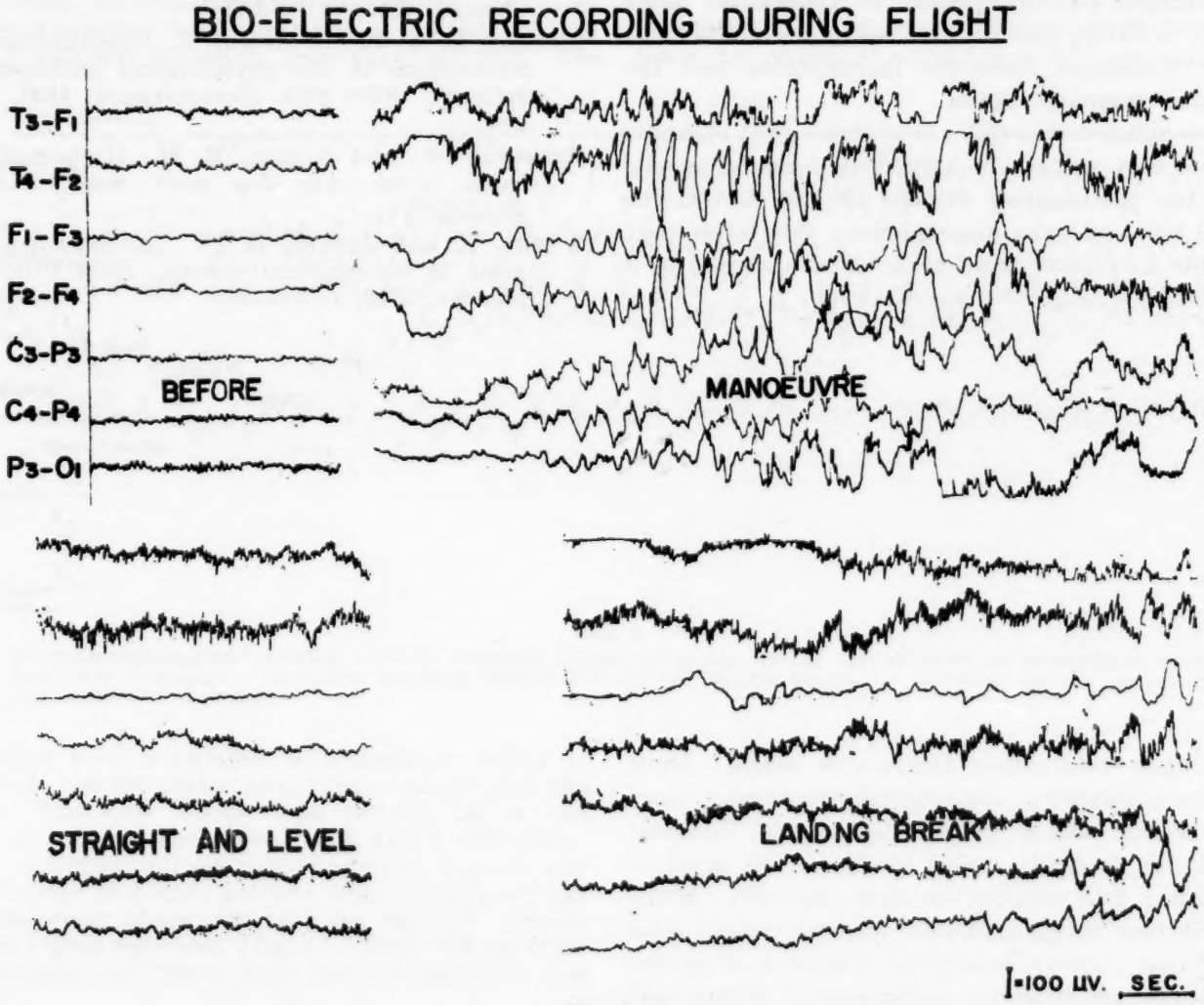

Fig. 1

Emotional factors are also known to be responsible for pilot errors.

Under combat flying, the pilot is subjected to a summation effect of a number of the factors mentioned above. In an attempt to obtain more information about the pilot under these circumstances, we decided to try a standard 8-channel EEG recording during rough operational flights.

With the kind co-operation of the Royal Norwegian Air Force, we have had a chance to try to

1 Read at the AGARD Meeting in Paris, France, June, 1958.

This research has been supported by the Royal Norwegian Air Force, Gen. Motzfeldt, Col. Nyby. Office of Scientific Research of the Air Research and Development Command, United States Air Force, through its European Office.

2 Since this paper was written 40 additional missions have been flown, and the preliminary findings have been substantiated.

solve the technical problems in a T-33. Dr. Frank Offner lent us an EEG transister apparatus, which was taken apart, modified, and mounted in various small places in the plane. It proved possible to obtain an EEG record during various types of operational flights. The unit tolerated an altitude of 20,000 feet, with a temperature as low as minus 45° centigrade. Neither the force of 8 Gs, rolls, nor other manoeuvres affected the instrumentation the first months.

Records have been made from pilots, and from non-pilots occupying the back-seat in the T-bird. The EEG tracing illustrated is recorded from an experienced pilot and shows startling information. Great changes were seen during some manoeuvres, and marked slow-waves appeared even during "Landing Brake".

The material thus far is small, but it is beginning to prove conclusively that a jet pilot's level of consciousness during operational flight varies and may be registered by standard EEG methods.

CONCLUSION

A new method for studying the stress to which jet fighter pilots are subjected has been demonstrated, and raises the questions: How competent are the pilots when they reach the target? Can we improve their alertness?

Reference: SEM-JACOBSEN, C. W., NILSENG, O., PATTEN, C. and ERIKSEN, O. Electroencephalographic recording in simulated combat flight in a jet fighter plane. *EEG Clin. Neurophysiol.*, **1959**, *11*: 154-155.

PRINTED IN CANADA

IS IT A TUMOR OR IS IT EYE MOVEMENTS?

A Method of Greatly Reducing Eye Movement Artefacts in the Frontal Leads

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(Received for publication: May 30, 1958)

One of the most difficult problems that faces the interpreter of EEG records is posed by the artifacts from eye movements. This problem is perhaps most important for patients around 45 to 60 years of age who have symptoms suggesting a brain tumor and perhaps a recent seizure or two.

Small, slow, irregular delta like waves in the frontals must, in such a case, be recognized with precision as intracranial or as eye movements.

There exists throughout the entire head a static field set up by the corneo-retinal dipole. This field (one for each eye) moves when the eyes move, resulting in a change of potential between any two points, depending upon how they are situated in this field.

Although the two leads to an amplifier remain equally far apart, it is possible to alter greatly the pickup of such field changes by changing the orientation of these leads or by changing their position on the head.

We have, since 1935, referred our leads to the vertex in routine cases. With such an arrangement the frontal to vertex and ear to vertex leads show vertical eye movements strongly, the occipital to vertex only moderately, and the central to vertex little or not at all.

Consideration of the lines in these fields suggests that there will be little change of the potential of the lines striking two points, one of which is nearly lateral to the other, when a vertical movement of the eyes is made. When the point usually used for frontal recording is referred to the midline (both in the same coronal plane), vertical eye movements are substantially absent in this channel.

Vertical eye movement waves with the eyes open (with vertex or ear used as a reference) are usually large and usually about equal in the two frontal areas and are in the same direction. When unequal the inequality remains about constant throughout the record. The rising phase is steeper than the falling phase. When the eyes are closed the movements usually stop, but in some people they do not stop but are much smaller and the waves resulting are greatly reduced in amplitude, but are often faster. Their rising and falling phases are similar and they resemble delta waves.

Horizontal eye movements produce waves which are usually in opposite directions in the frontal leads and are often unequal. (It seems likely that the eyes do not always move together when closed.)

Although eye movements cause trouble only in a few people, they are sometimes most difficult to evaluate and the electroencephalographer must decide with reasonable confidence whether the waves he sees are due to eye movements or are from an intracranial source.

There are several ways of approaching this decision: (1) If the eyes are left open, most of the waves resulting from eye movements are of the large, vertical type, which rise rapidly and fall a little more slowly and are about equal in the two frontal areas. The space between these large waves is usually free from the smaller delta-like waves caused by eye movements when the eyes are closed.

(2) Theoretically eye movement waves will disappear when the eyes are not moved. No one can avoid blinking his eyes when they are open but some people move them with surprising rapidity when they are closed, making waves as fast as 6 per sec., which are often sinusoidal and delta-like in appearance. These waves are of much lower amplitude than those seen when the eyes are open and become thereby even more readily confused with waves from tumors. These jittery people do not know that their eyes are moving and the movements can be sometimes stopped by placing nickels on the lids. This allows them to feel the movements of their eyes. The same result is perhaps a little more easily achieved by letting them press their fingers lightly in the corners of their eyes.

(3) When two leads are placed horizontally in the same coronal plane the channel to which they are connected shows little or no response to even large vertical movements of the eye field. Thus, if one places an electrode in the midline directly medial to the frontal lead from which questionable waves are coming, this pair of electrodes will not show vertical eye movements in a substantial amount, and as about 90 per cent of movements made with the eyes closed are vertical, being blinks and flutter movements, the problem of eye movements will be largely resolved by

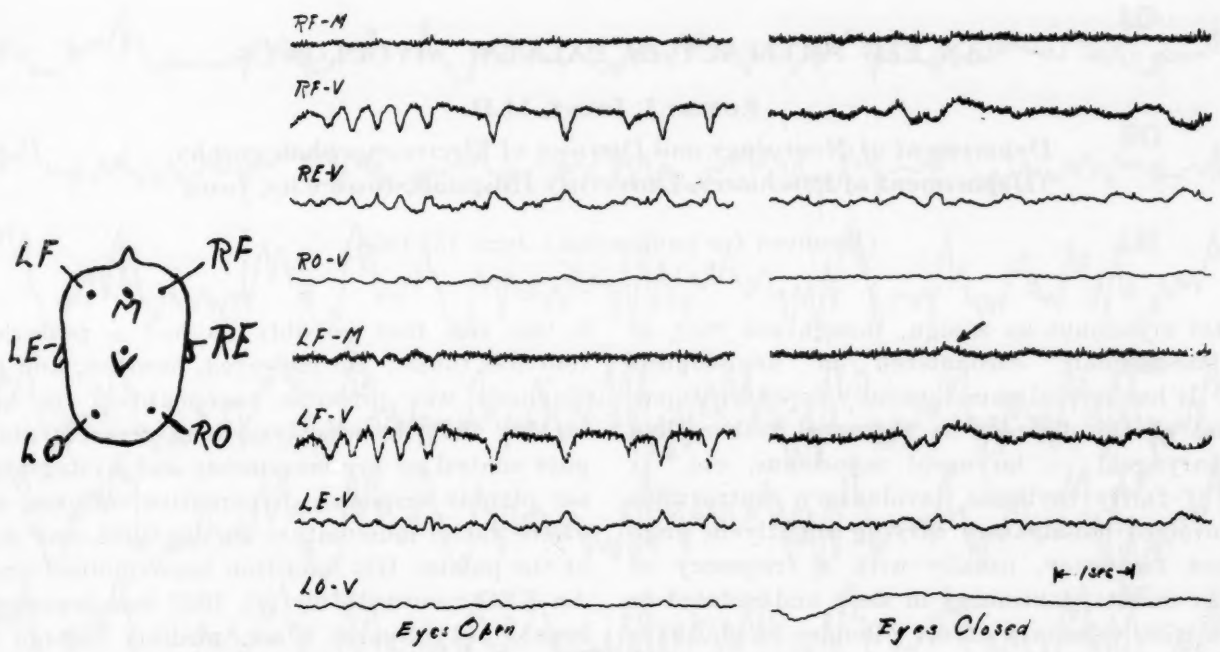

Fig. 1

This poorly relaxed person made many eye movements both with eyes open and closed. The vertical eye movements are almost absent from the frontal to mid-line derivation. At the arrow there is presumably a horizontal component to the eye movement.

this placement. Horizontal eye movements produce as large a voltage in this placement as in most other placements but they occur much less commonly.

The delta waves due to frontal tumors appear just as well in this frontal to midline placement as when the frontal is referred to any other region.

SUMMARY

Frontal EEG waves resulting from vertical eye movements can be largely eliminated by using a frontal to midline derivation in which both electrodes are in the same coronal plane. Such a derivation shows the delta waves due to tumors well.

Reference: CASE, T. J. Is it a tumor or is it eye movements ? *EEG Clin. Neurophysiol.*, **1959**, *11*: 156-157.

PRINTED IN CANADA

AN EEG ARTEFACT IN PALATAL MYOCLONUS

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(Received for publication: June 15, 1958)

Palatal myoclonus as a sign, though not rare, is rather uncommonly encountered in neurological diseases. It has several names, usually dependent upon the extent of the disorder as laryngeal rather than palato-pharyngeal — laryngeal myoclonus, etc. It consists of fairly rhythmic, involuntary contractions of the involved musculature varying slightly in amplitude and frequency, usually with a frequency of 50-240 per minute, continuing in sleep and reduced or abolished with voluntary effort (Bender *et al.* 1952; Brock 1953). Bender, Nathanson and Gordon list the following muscle groups involved in order of frequency; palate, pharynx, larynx, eyeballs, corner and floor of the mouth and diaphragm. The usual locus of the nervous system lesion to be responsible for this disorder is an interruption of fibers anywhere in the triangle constituted by the inferior olive, dentate nucleus and red nucleus (Guillain and Mollaret 1931).

This condition is quite easily recognized when the abnormal movements are wide-spread and excessive so that the facial musculature is involved. At this point, the clinician can diagnose it at a glance and the electroencephalographer can see the prominent muscle potentials. However, when it involves the palate and/or pharynx only, it may be easily overlooked by the examiner and constitute a confusing source of artefact for the electroencephalographer. Two such patients are briefly reported along with the EEG findings, one a probable case of encephalitis and the other an invasive tumor of the cerebellum.

METHOD

The electroencephalograms were recorded with a Grass Model III A 8 channel electroencephalograph. Both bipolar and monopolar with separate and joined ear references and vertex references were used.

CASE REPORTS

Case 1. This 27 year old man was admitted to the Veterans Administration Hospital May 16, 1957. He first became ill in April 1956 with headaches and progressive ataxia. In November 1956, lumbar puncture and air studies were performed and a diagnosis of encephalitis was made. He became progressively more lethargic and was admitted to the University Hospital, Iowa City. Air studies were repeated and it was felt that possibly he had a posterior third ventricle tumor. He improved, however, and the final diagnosis was probable encephalitis. On admission in May 1957, he was dysarthric, severely ataxic, had poor control of eye movements and nystagmus, extensor plantar responses, hyperactive reflexes, weakness of the facial musculature on the right, and myoclonus of the palate. His condition has remained unchanged. An EEG recorded July 30, 1957 was reported as follows: "(1) Sparse 9/sec. medium voltage occipital alpha; (2) diffuse 3-4/sec. medium and high voltage activity slightly more prominent on the right; (3) recurrent spike at about 180/min., most prominent in monopolar leads. Impression: Record is diffusely slow with slight lateralization to the right. The 180/min. spike activity could possibly be a recording of electromyogram of palatal myoclonus." An EEG run September 23, 1957 was the same; however, natural sleep recording was done and the spike activity was evident during sleep (see fig. 1).

Case 2. A 33 year old male was first admitted to the Veterans Administration Hospital on June 12, 1957, complaining of headaches and vomiting. He first developed these symptoms in December 1955 and gradually became ataxic. A ventriculogram was performed in April 1956 and was followed by a suboccipital craniectomy. The right cerebellar hemisphere was swollen, and a Torkildsen procedure was done. He had some improvement until a few weeks prior to his June 1958 admission. Initial examination revealed slurred speech, inability to look to the right, severe ataxia, and tenseness of the craniectomy site. He gradually became more lethargic until it was necessary to perform a ventricular tap and ventriculograms were repeated and demonstrated an internal hydrocephalus with displacement of the fourth ventricle to the left. The site was re-explored and most of the right cerebellar hemisphere was removed. The pathological report was a malignant glioma. He received radiation therapy to this region with some improvement. He was re-examined in October and December of 1957. On these admissions, he had inability to look to the right, weakness of the right facial musculature, reduced alternating motion rate of the tongue, and severe ataxia. It was also noted that he had palatal myoclonus along with the subjective complaint of clicking in the ears. An electro-

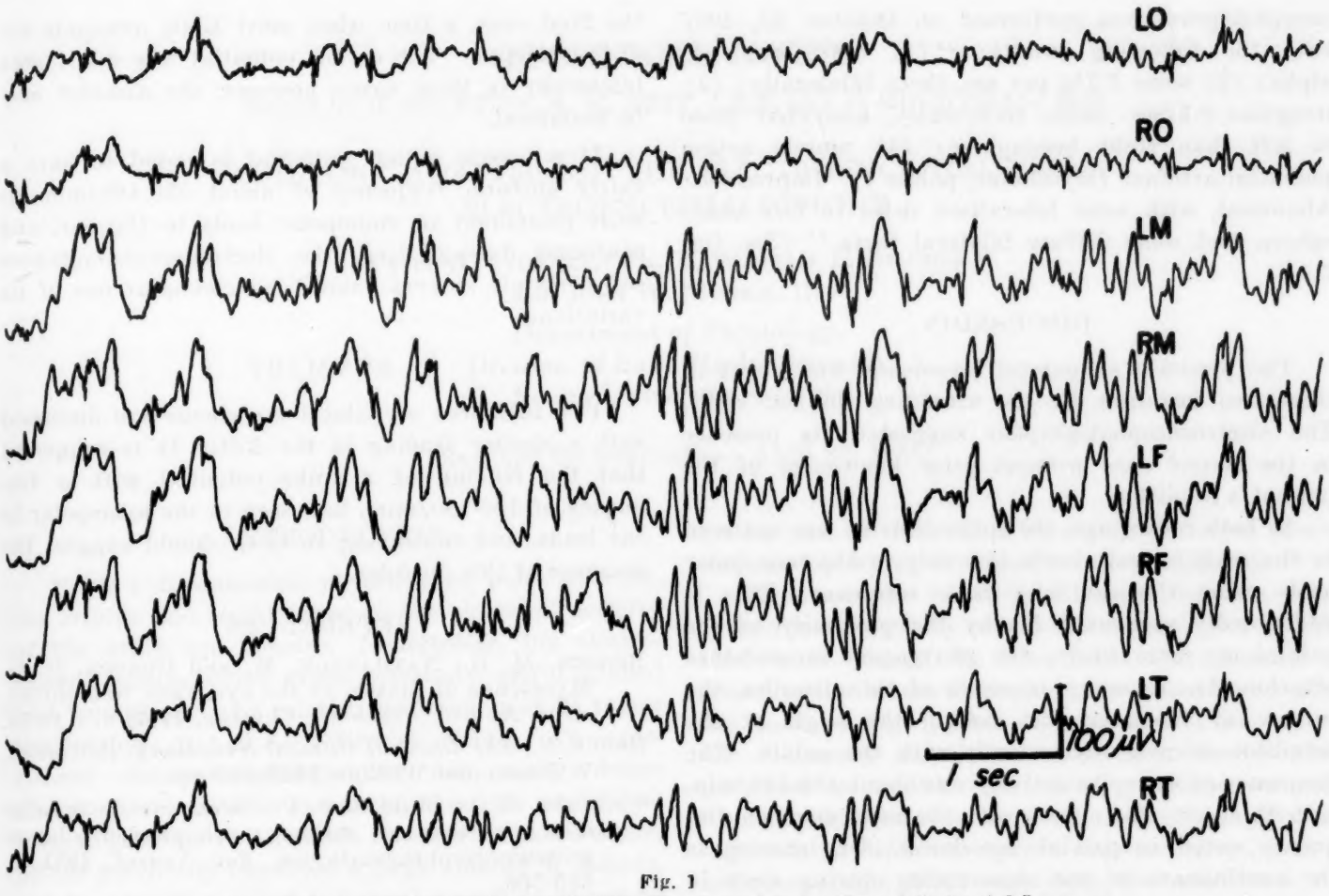

Fig. 1
Sleep record of patient with encephalitis. Note prominent spike artefacts at 2.5 per sec.

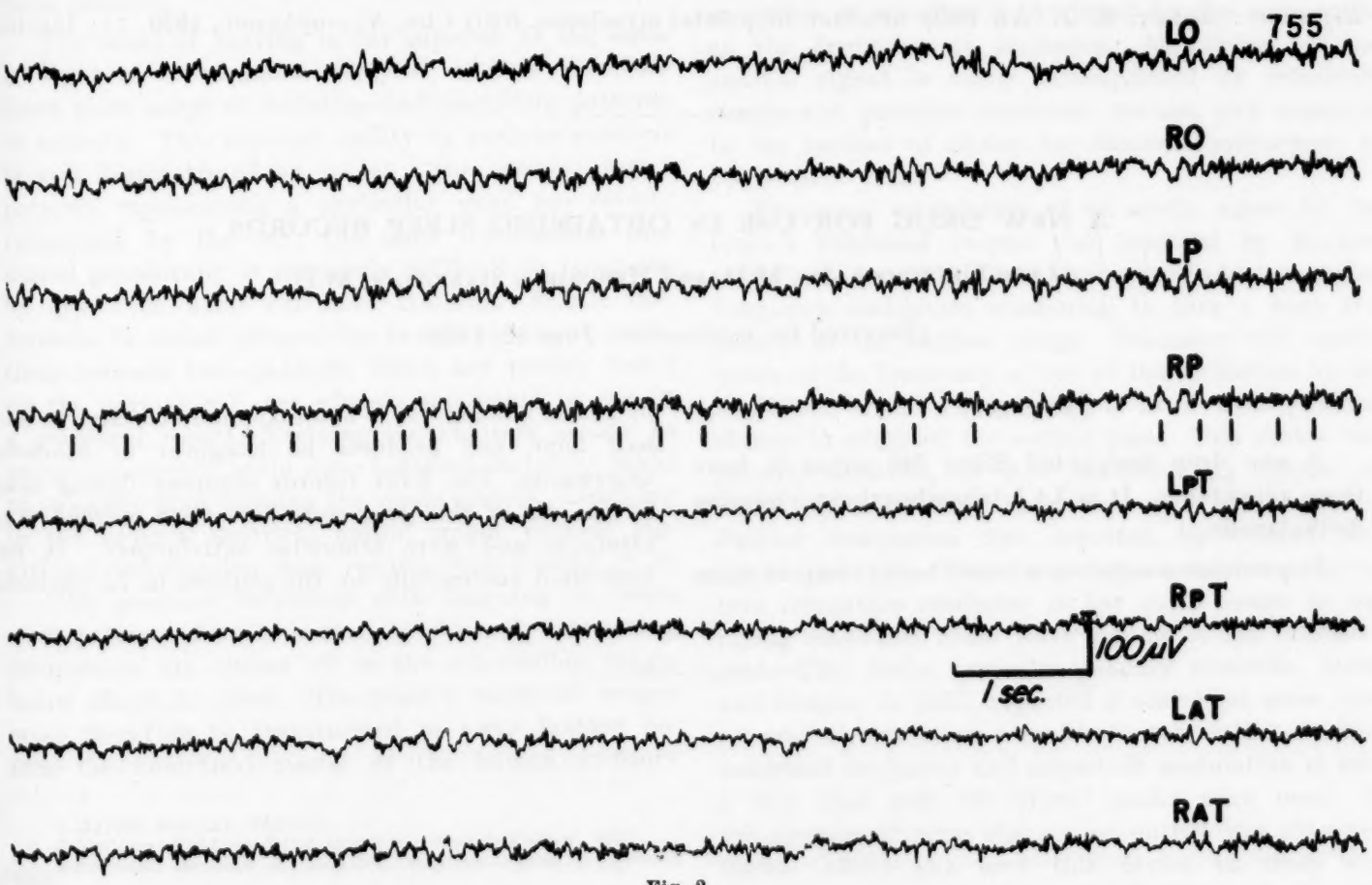

Fig. 2
Waking record of patient with invasive cerebellar tumor. Some of the muscle artefacts marked in channel 4. The frequency varies from 3 to 4 per sec.

encephalogram was performed on October 23, 1957 with the following results: "(1) 8-8½ per sec. alpha; (2) some 7-7½ per sec. theta bilaterally; (3) irregular 2-3/sec. delta, recurrently, somewhat more in left than right hemisphere; (4) muscle action potential artefact (myoclonus, palate ?). Impression: Abnormal, with some lateralized delta in left hemisphere, and some diffuse bilateral theta." (See fig. 2.)

DISCUSSION

The presence of palatal myoclonus was noted in these two instances by the attending clinical staff. The electroencephalographer suggested its presence in the second case without prior knowledge of the patient's condition.

In both recordings, the spike activity was not seen in the scalp-to-scalp leads but only in the monopolar leads using the ear lobe as a reference. This is undoubtedly accounted for by the proximity of the palatal or, more likely, the pharyngeal musculature attachments. In many examples of this disorder, the surface of the neck just behind the angle of the mandible retracts rhythmically with the palate. The frequency of the spike activity was about 150-180/min. in both cases; this agrees with the most common frequency noted in palatal myoclonus. Of interest, is the continuance of the abnormality during sleep in the first case, a time when most EMG artefacts are at a minimum. The action potential was distributed bilaterally in these cases, however, the disorder may be unilateral.

If a muscle action potential is noted to have a fairly uniform frequency of about 150-180/min., is most prominent in monopolar leads to the ear, and continues during sleep, the electroencephalographer can certainly suspect palatal myoclonus or one of its variations.

SUMMARY

Two instances of palatal myoclonus are discussed with a similar finding in the EEG. It is suggested that the finding of a spike potential with a frequency of 150-180/min., best seen in the monopolar to ear leads, and continuing in sleep should suggest the presence of this disorder.

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A NEW DRUG FOR USE IN OBTAINING SLEEP RECORDS

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(Received for publication: June 12, 1958)

(Abstract)

A new drug designated Riker 548 seems to have these advantages. It is 3,4,5 trimethoxybenzoylglycine diethylamide.

It produces a sedation without heavy sleep in doses of 250 to 900 mg. It is non-toxic and effective in one-half hour, and produces no hangover or headache afterwards. The EEG records obtained during sleep by the use of this drug were free from marked drug artefacts and were otherwise satisfactory. It has been used successfully by the authors in 53 patients.

PRINTED IN CANADA

TECHNICAL NOTES

Edited by H. SHIPTON, A. M. BRIT, I.R.E. and F. BUCHTHAL, M.D.

AUDITORY ANALYSIS OF THE ELECTROENCEPHALOGRAM: ELECTROENCEPHALOPHONY

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(Received for publication: April 20, 1958)

INTRODUCTION

From a fundamental physiological point of view, the origins and significance of the electrical activity of the brain are obscure. Nonetheless, the electroencephalogram serves as an extremely useful clinical tool in epilepsy and related disorders, and in tumor localization (J.A.M.A. Editorial 1954). An experienced electroencephalographer can easily detect characteristic patterns and variations from established normal patterns in an EEG. He can do this because he has previously inspected a large number of records, and has thereby trained his visual system to recognize these patterns.

The sense of hearing is far superior to the sense of sight as a harmonic analyzer, and is therefore much more adept at detecting and analyzing patterns of activity. This superior ability to analyze patterns is well demonstrated by speech. The complex sound patterns representing a particular word are readily recognized by the ear; the same information presented graphically is extremely difficult to recognize by eye, even after extensive training. Subtle differences in sound pattern due to age or accent variations between two speakers, which are readily heard by the normal ear, are almost impossible to see in a graphical record. Training the auditory system to recognize specific brain wave patterns therefore ought to be easier than training the visual system. Listening to the brain's electrical output might provide significant information more readily than looking at it.

The practical difficulty with listening to brain wave patterns directly is that the clinically interesting frequencies are almost all in the sub-audible range, below about 30 c/sec. The brain's electrical output must therefore be transformed in some fashion before the analytical merits of the human auditory system can be utilized. This report describes several methods by which this has been accomplished.

There are two basically different ways to transform a low frequency sound into an audible one. The first is to change the time base, for example, by recording on magnetic tape at slow speed and playing back at high speed. The second is to use the low frequency signal to modulate a device which generates an audible tone; either frequency or amplitude modulation can be used. Recording and playing back at different speeds require expensive magnetic tape equipment and have the additional disadvantage that the duration of significant events such as spikes or spindles is shortened by the same ratio as the frequency is increased. Modulation of an audible signal is easily accomplished by relatively simple and portable electronic devices, and seems to be the method of choice for clinical applications at the present time.

Frequency modulation of an audio signal by the brain's electrical output was reported by Beevers and Furth in 1941. Their device involved two radio-frequency oscillators combining to give a beat frequency in the audible range. Reactance-tube modulation of the frequency of one of the oscillators by the amplified brain waves resulted in a corresponding change in pitch of the output tone. This device was polarity sensitive, so that positive-going signals resulted in increasing frequency and vice-versa. A simpler instrument was reported by Conrad and Pacella in 1947. They frequency modulated a thyratron relaxation oscillator in the audio range by applying amplified brain wave signals to the thyratron grid. This device was also polarity sensitive. Bates and Cooper, in 1955, reported a somewhat more complicated circuit using a multivibrator oscillator which combined frequency and amplitude modulation in such a way that only the signal peaks were used. In the absence of large signals, no output was obtained. Bates (1953) has used this device to study cor-

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1 Markle Scholar, 1956-61.
2 National Tobacco Fund summer research Fellow, 1957.
3 National Science Foundation summer research Fellow, 1957.

relations between speech and abnormal EEG states. An amplitude modulation instrument was reported by Kozevnikov and Soroko in 1956. It was based on the fact that an audio tone injected into the common cathode circuit of a conventional balanced push-pull audio amplifier stage appears in the output only

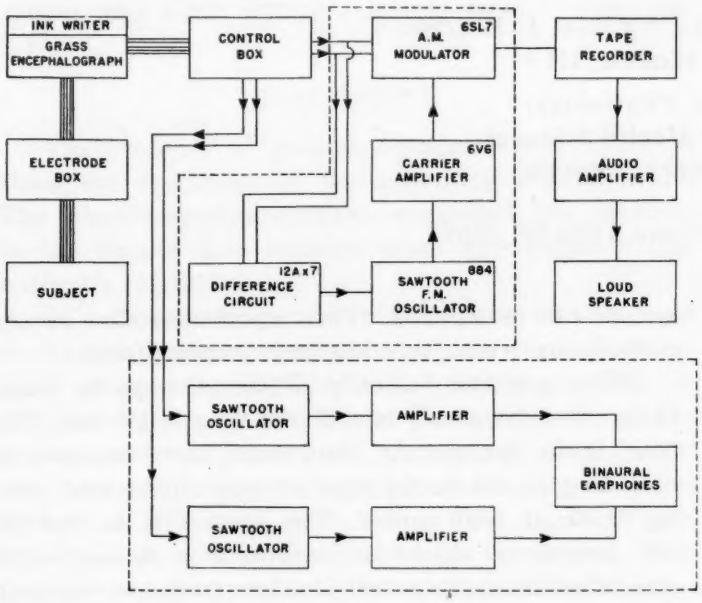

Fig. 1

when the stage is unbalanced by virtue of a signal applied between two grids. Using the brain waves as input signal to such a circuit, they obtained an output at a single frequency, the amplitude of which varied with the amplitude of the brain waves. This device was not polarity sensitive.

In order to evaluate the merits of these various methods of electroencephalophony, several instruments similar to those described above were constructed in this laboratory. Our version of the beat frequency oscillator of Beevers and Furth suffered from frequency drift and interlocking of the oscillators, and was discarded. A relaxation oscillator similar to that of Conrad and Pacella was found to be highly satisfactory. The amplitude modulation system of Kozevnikov and Soroco was improved by using a frequency modulated relaxation oscillator as the audio source. The resulting combined amplitude and frequency modulated unit has been used as the basic instrument in most of our studies.

INSTRUMENTATION

Figure 1 is a block diagram of the electroencephalophone system, and figure 2 is a detailed circuit diagram of the combined amplitude and frequency modulated instrument (hereafter referred to as the AM-FM encephalophone or EEP). A balanced output signal from each channel of the inkwriting electroencephalograph recorder is taken from the grid circuits of the power amplifier stage, and led to a control box which sits on or beside the EEG recorder. Any desired EEG channel can then be selected by the control box selector switch, and fed into the EEP. All connections between the EEG, control box and EEP are made by Jones plugs or standard 3-connector phone plugs and jacks, and shielded cable. The selector switch is mounted in its own box instead of in the EEP in order to minimize the number of wires trailing around the EEG room, and to permit the EEP to be located at a distance from the EEG.

The EEP circuit itself (fig. 2) has two basic parts, the AM channel and the FM channel. The

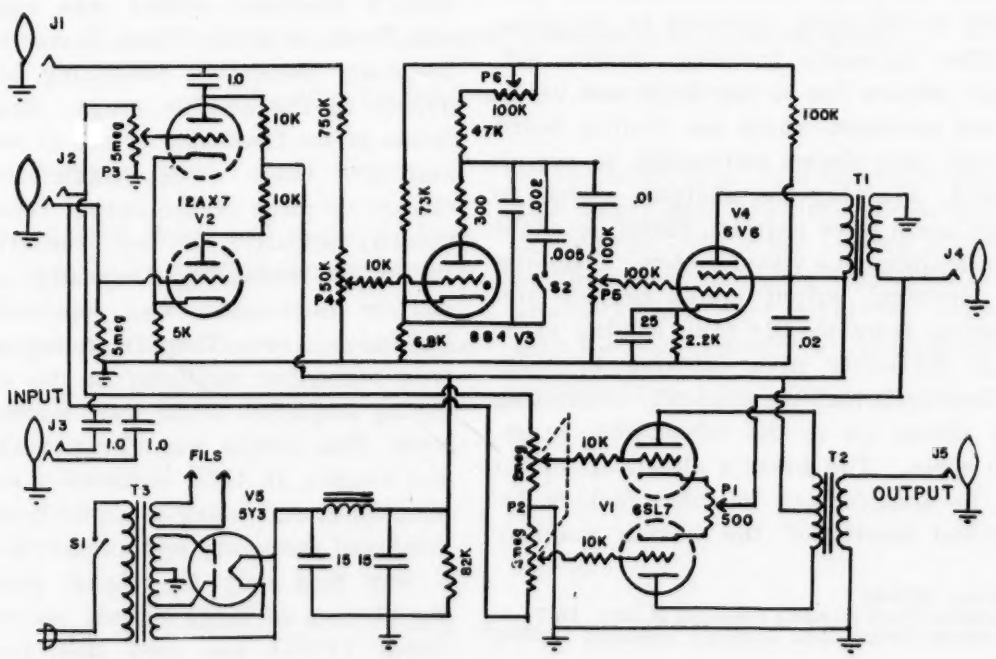

Fig. 2

AM channel consists of the conventional push-pull amplifier V_1 driving the output transformer T_2. The balancing potentiometer P_1 and the secondary winding of the coupling transformer T_1 constitute the common cathode load of V_1 by means of which an audio carrier signal of any selected frequency from the oscillator circuit can be impressed on the two cathodes. With P_2 set for zero signal on the grids, P_1 is adjusted to balance the circuit, and no output at carrier frequency is obtained. Any differential signal applied to the grids will then unbalance the circuit, so that carrier frequency will appear in the output. The amplitude of the output signal measures the amplitude of the input signal. Jack J_4 allows an external supplied carrier tone to be used if desired.

The FM channel consists of the thyratron relaxation oscillator V_3 and power amplifier V_4. The circuit of V_2 is a difference circuit to convert from push-pull to unbalanced signal. FM-operation alone is achieved by setting P_2 to zero, applying the brain wave signal to the grid of V_3 at appropriate amplitude determined by the setting of P_4, and unbalancing the output circuit by means of P_1. Balancing P_1 and turning up P_2 appropriately results in amplitude modulation of the frequency modulated carrier, or combined AM-FM operation.

Conventional audio amplifiers, speakers and tape recorders are used to monitor and record the output signal. Jack J_1 provides a single-ended brain wave signal for monitoring the brain waves directly, without any modulation. A push button shorting switch can be plugged into Jack J_2 to provide a marker signal in the record at any desired time. When the EEP is used in conjunction with an inkwriter, this arrangement also inserts the marker signal into the written record.

As indicated in figure 1, two additional separate FM channels using thyratron oscillator circuits are provided for connection to earphones, for binaural studies.

A wide range of base carrier frequencies has been tried. The band from about 800 to 1,000 c/sec. is the most pleasant to hear, but a base frequency close to 2,000 c/sec. is more efficient in terms of identifying patterns. Since the EEP does not have the frequency bandwidth limitations of an inkwriter, we plan to use a much wider bandwidth amplifier system in place of the standard EEG amplifiers in future work.

RESULTS AND DISCUSSION

The sound of the output from the EEP when brain waves are fed into it is difficult to describe verbally. In general, amplitude modulation alone is not very satisfactory. The chief difficulty is that it is not polarity sensitive, so that the apparent frequency of repetitive signals such as the alpha waves is twice the actual frequency. Frequency medulation alone permits the ear to follow the EEG tracing very easily, and to pick out characteristic patterns as they occur. The only objection to FM alone is the constant background level, regardless of signal intensity, which becomes distinctly unpleasant after a brief period of listening. Combining the amplitude and frequency modulation operations eliminates both of the difficulties, and provides a very sensitive method of analysis of brain wave patterns. With very little practice, characteristic patterns can be readily detected by ear, and recognized whenever they occur.

The alpha rhythm in the occipital leads is one of the most easily detected EEG patterns. Connecting an occipital lead to the EEP results in characteristic pulsating vibrato-like output, as might be expected. This alpha wave pattern is in fact much easier to detect and to follow audibly than visually on the EEG tracing. This is particularly true if the amplitude of the alpha waves is very small, so that they are often visually indistinguishable from the background activity. They can still be clearly distinguished audibly under these conditions.

While it is true that rhythmical activity will always be most easily distinguished by the ear, there is a large number of other characteristic EEG patterns and waveforms which are also clearly distinguishable audibly, and which stand out, even on first listening. For example the spike and dome type of pattern which occurs in petit-mal epilepsy has an unmistakable sound, and can be detected easily, even by a novice. As rapidly as clinical material becomes available, we are accumulating EEP tape recordings from patients and normal subjects, to study the correlations between the EEG and the EEP records, and to discover what additional contributions this technique can make to the interpretation of brain wave patterns.

The EEP also permits a subject to monitor his own brain waves. We have found that when one attempts to listen attentively to his own alpha rhythm, it disappears. Casual listening results in its return. This might have been expected, since it is well established that disappearance of the alpha rhythm is correlated with concentration (Darrow 1957). The procedure suggests that the EEP provides an important tool for the direct investigation of the subjective phenomena of concentration and attention.

Bates and Cooper, and Beevers and Furth have previously pointed out the advantages of being able to monitor the EEG while attending to the subject or carrying out an experimental procedure. We have found the EEP sufficiently useful as a monitor that we would recommend its routine use in conjunction with standard EEG's. An additional advantage is

that if the EEP output is recorded on magnetic tape, a microphone can be used to insert into the recording any desired information about the state of the subject, movements likely to cause artifact, or experimental procedures. Furthermore, monitoring applications are not restricted to brain waves. By virtue of its frequency transforming characteristics the EEP is useful also for monitoring electrocardiograms, electroretinograms, and other bioelectric signals.

Several attempts were made to detect phase differences between brain waves from two sides of a subject's head by means of the binaural FM system. These observations have yielded inconclusive results to date, but many potentialities for this binaural EEP technique remain to be investigated.

One of the advantages of the written EEG record is that it converts the time dimension to a space coordinate so that short-duration waveforms such as spikes can be inspected carefully after they have occured. A disadvantage to any listening device is that isolated very rapid changes in pitch and amplitude may not be accurately perceived and evaluated. It would therefore be desirable in conjunction with the EEP to use a multispeed tape recorder so that the AM-FM record could be played back much more slowly than it was recorded, in order that complex patterns could be more carefully analyzed. For these purposes a base frequency of from 20,000 to 40,000 c/sec. and a tape speed ratio of 20 or more to 1 are probably indicated.

SUMMARY

1. Since the ear is a better harmonic analyzer than the eye, a technique which makes it possible to listen to brain waves might provide significant information more easily than looking at EEG records.

2. Due to their sub-audible frequency spectrum, brain waves must be transformed in some fashion to be made audible. Combined amplitude and frequency modulation of an audio carrier by the brain waves provides a highly satisfactory method. The circuit of an AM-FM encephalophone (EEP) for accomplishing this is described.

3. Brain waves result in characteristic sound patterns from the EEP, and these patterns are detected and recognized very easily, as predicted. The EEP is recommended as a routine supplement to the standard EEG, both as a monitor, and to aid in the analysis of records.

4. The use of the EEP as a convenient tool for studying concentration and attention phenomena is suggested by the results of experiments in which subjects monitored their own alpha rhythms.

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PRINTED IN GREAT BRITAIN

A MULTIELECTRODE LEAD FOR INTRACEREBRAL RECORDINGS [1]

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(Received for publication: May 13, 1958)

The features of the electrodes used for intracerebral recordings have gradually evolved since the first subcortical recording was obtained from a human being by Berger in 1931. The evolution of such electrodes concerns the structure peculiar to them as well as the purpose they serve. In fact, in recent years intracerebral recordings once obtainable only during intracranial operations have been replaced by more complete studies conducted by means of electrodes implanted over a long period within the substance of the brain.

ELECTRODES FOR "ACUTE" IMPLANTATION

The electrodes used for "acute" intracerebral implantation in human beings may be divided into essentially six types:

1. Single needles (Berger 1931; Monnier 1952).

2. Double needles (Jung, Riechert and Meyer-Mickleleit 1950; Monnier 1952).

3. Concentric electrodes made of an outside needle and of an inside wire or stylet (Wada, Endo and Marui 1950; Jung, Riechert and Heines 1951).

4. Electrodes made of multiple strands of wire contained in a brain needle (Walter and Dovey 1946; Gastaut 1949; Williams and Parsons-Smith 1949) or held in a plexiglass container (Jung, Riechert and Heines 1951; Von Baumgarten 1953) or in a polyethylene tube (Spiegel, Wycis, Baird and Szekely 1956) through which the tips of the electrodes protrude.

5. Multielectrode needles with the electrodes arranged in the form of rings separated by insulating material (Hayne, Belinson and Gibbs 1949; Bickford, Uihlein and Petersen 1953; Dell, Talairach, Lairy-Bounes and Dell 1952; Okuma, Shimazono and Narabayashi 1955).

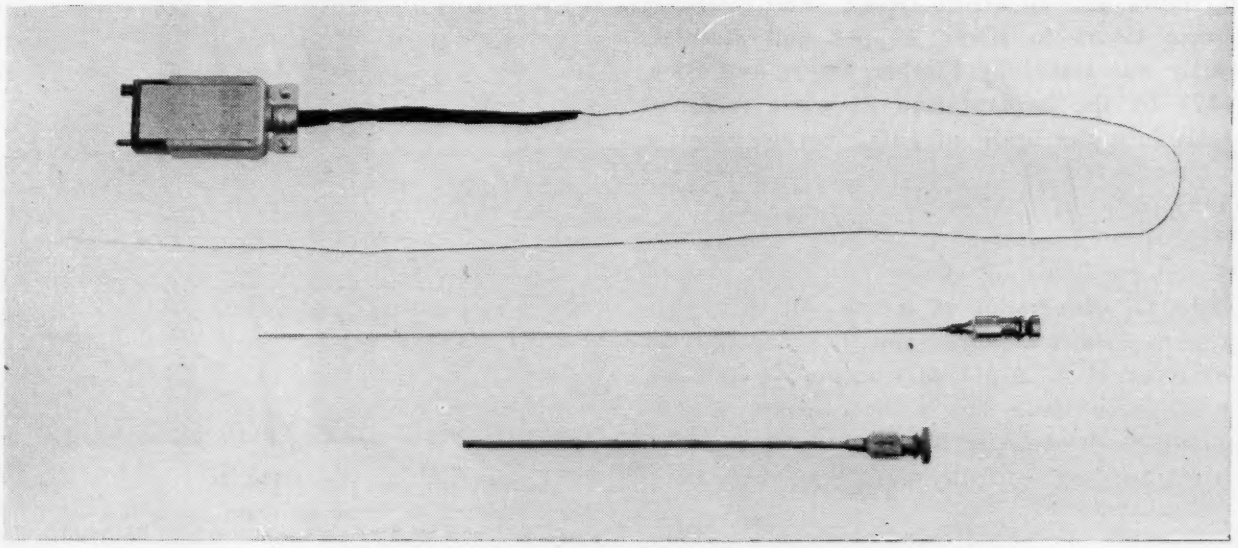

Fig. 1

From bottom to top are: a common brain cannula, the introducer and one multielectrode lead used in the authors' investigations. This is connected to a miniature receptacle.

6. Leads made of single strands (Lennox and Ruch 1946) or of multiple strands of wire bound together (Bickford, Uihlein and Petersen 1953) introduced through a needle, to be removed after implantation of the leads.

1 This study was supported in part by a research grant to the Rochester State Hospital from the Minnesota Department of Public Welfare.

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ELECTRODES FOR "CHRONIC" IMPLANTATION

Four fundamental types of electrodes were used for "chronic" intracerebral implantation:

1. Single strands of wire soldered to a small terminal ball (Heath 1954).

2. Multiple strands of wire bound together to form a shaft (Delgado, Hamlin and Chapman 1952; Dodge, Holman, Sem-Jacobsen, Bickford and Petersen 1953; Heath 1954).

3. Multiple strands of wire cemented together with plexiglass (Heath 1954; Delgado and Hamlin 1956).

4. Multiple parallel needles (Chapman, Schroeder, Geyer, Brazier, Fager, Poppen, Solomon, Yakovlev 1954).

In the course of the development of depth-recording technique, various metals have been used for depth electrodes, but silver is chiefly used (Berger 1931; Walter and Dovey 1946; Williams and Parsons-Smith 1949; Hayne, Belinson and Gibbs 1949; Monnier 1952; Von Baumgarten 1953; Bickford, Uihlein and Petersen 1953; Heath 1954; Okuma, Shimazono, Fukuda and Narabayashi 1954; Spiegel, Wycis, Baird and Szekely 1956; Delgado and Hamlin 1956); copper (Lennox and Ruch 1946; Gastaut 1949; Bickford, Uihlein and Petersen 1953; Dodge, Holman, Sem-Jacobsen, Bickford and Petersen 1953; Heath 1954). Stainless steel also has been employed (Delgado, Hamlin and Chapman 1952; Baldwin, Frost and Wood 1954; Dodge, Petersen, Sem-Jacobsen, Sayre and Bickford 1955). The tolerance of the brain tissue to silver, copper and stainless steel recently was tested by Fischer, Sayre and Bickford (1957) by the implantation of wires made of these metals into the brain of cats. Severe reaction and necrosis of brain tissues, provoked by silver and copper, were only minimal when stainless steel was used. Therefore, the inertness of stainless steel makes it one of the materials of choice for depth electrography from the standpoint of safety. In the course of the same experiments polyethylene, tygon, formvar and thermobond M — 472 insulations were well tolerated by the brain tissue. The formvar appeared to be the most suitable because it is easily applied and it does not require any complicated processing procedures.

The gauge of the wires used for depth electrodes has been gradually decreased since the beginning of depth recording in human beings. Recently, 46-gauge (Sem-Jacobsen, Petersen, Dodge, Lazarte and Holman 1956) and even 52-gauge stainless-steel wire has been used in our laboratory. However, it was later found that some degree of increase in the interelectrode impedances and in the fragility of the depth leads resulted from the use of these small wires. The 40-gauge (0.0031 in.; 77.5 microns) or the 42-gauge (0.0025 in.; 62.5 microns) size appeared to be the most satisfactory for our work.

The experience of the previous authors has been of great help to us in designing our intracerebral leads. In fact, our leads have some features in common with those described by some of us a few years ago (Dodge, Holman, Sem-Jacobsen, Bickford and Petersen 1953) and with those used more recently by Chapman (1957). They consist of 7 or 13 strands of type 316, 40-gauge (0.0031 in.; 77.5 microns) or 42-gauge (0.0025 in.; 62.5 microns) formvar insulated stainless-steel wires twisted together to make a shaft. The end of one strand is bared for a distance of 1 mm. This end wire is wound in spirals around the stylet of an introducer,

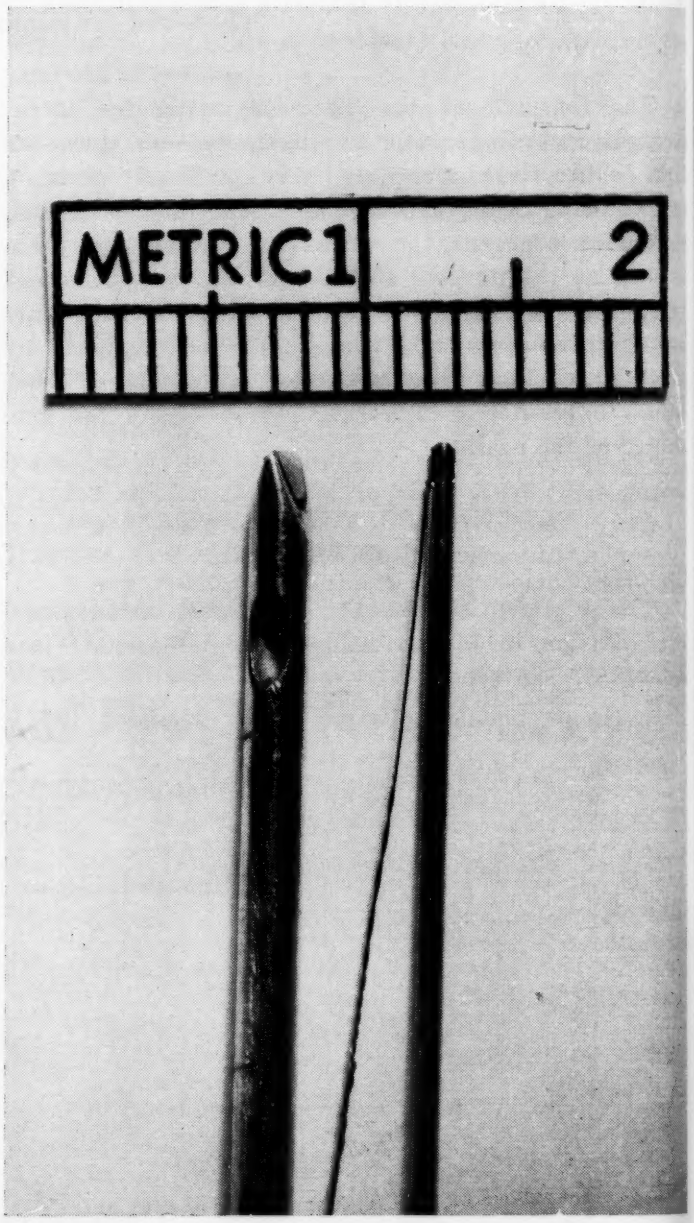

Fig. 2

Extremities of a common brain cannula (left) and of a multielectrode lead (right). The coiled extremity of the lead is supported by the stylet of the introducer.

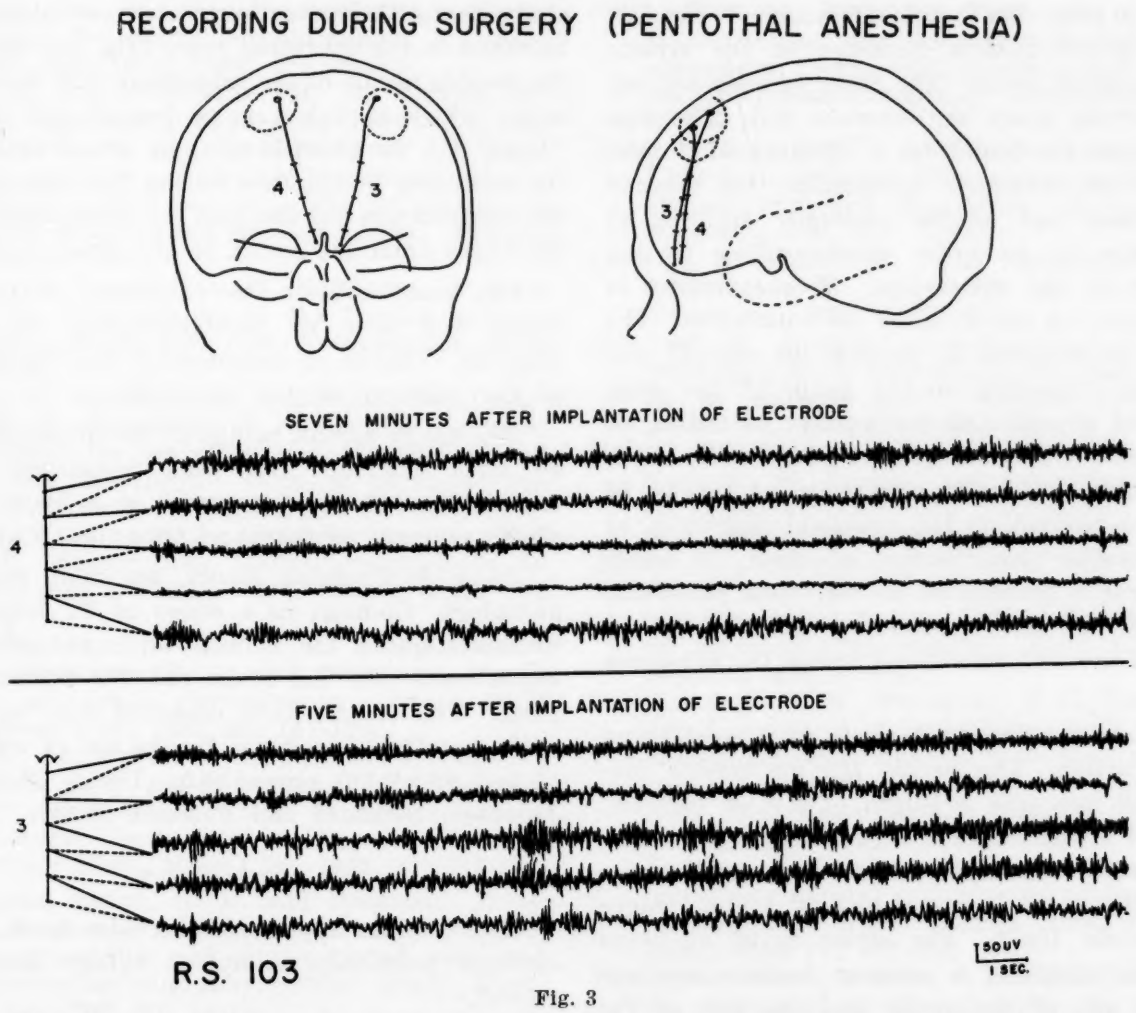

Fig. 3

Recordings obtained in the operating room shortly after implantation of each of two six-electrode leads into the frontal lobes preceding prefrontal lobotomy (same patient as the one concerned in figure 4).

Fig. 4

Posteroanterior and lateral roentgenograms of the skull show eight multielectrode leads implanted into the brain, in this instance preceding prefrontal lobotomy.

resulting in a coil. The inside diameter of the coil corresponds to the outside diameter of the stylet; the length is about 1 mm. The other strands are cut at 1-cm. intervals above the terminal coil. The tips of these strands are bared for a distance of 1 mm. For purposes of conductor recognition, the strands of the proximal end of the electrode are cut at different levels in an order corresponding to the one followed for the distal tips. This extremity is bared for about 1.3 cm. to allow for connection. The total length of the lead is between 45 and 47 cm. The diameter, depending on the gauge of the wire, the number of strands and the number of twists, is, in the case of our seven-strand, 40-gauge lead, about 0.28 mm. A special code consisting of marks of colored tygon painted at the proximal extremity of the leads permits identification of them. A white mark of tygon is painted at 15 cm. from the distal extremity of the lead, permitting measurement of the length of the lead introduced within the substance of the brain.

The introducer (fig. 1) consists of a needle and stylet combination. The needle has an outside diameter of 0.89 mm. and a length of 9.9 or 19.9 cm. It is soldered to the hub of a regular 22-gauge lumbar puncture needle. The stylet is 0.56 mm. in diameter and 10 or 20 cm. in length, which is 1 mm. longer than the needle itself. The stylet is in all ways similar to the stylet of a common lumbar puncture needle. The hub of the needle and the hub of the stylet can be secured by means of a bayonet-type lock which consists of an L-shaped slot cut in the hub of the needle and a corresponding metal projection soldered into the hub of the stylet.

Before the instrument is introduced into the substance of the brain the stylet is secured in place with the needle. After this, the tip of the stylet, which emerges for a distance of 1 mm. from the end of the needle, is inserted into the terminal coil of the lead (fig. 2). Since the coil has about the same outside diameter as that of the needle, the two surfaces are practically continuous. During introduction the coil is supported by the tip of the stylet, and when the lead has reached the position desired by the surgeon, the hub of the stylet is disengaged from the hub of the needle and is slightly retracted, so that the coil is deprived of its support. At this point the lead is completely independent from the introducer, which may be withdrawn.

Since the lead is not inserted into the substance of the brain through the needle introducer but rather external to it, it is possible to connect the lead before surgery to a miniature receptacle (fig. 1). In this manner, by simply plugging into this receptacle the corresponding plug of an extension cable, the electrodes can be connected to the input of the electroencephalographic apparatus and recordings can be taken in the operating room (fig. 3). In addition, the outside needle of the introducer may be covered by tygon which is baked at a temperature of 330°F. (165.4° C.) for 25 to 30 min., an action which permits the recording of tracings during the various steps of the introduction of the lead by preventing electrode shortages from the cortex to the final position.

The small coil at the extremity of the lead is fairly well seen in roentgenograms of the skull (fig. 4). This is of considerable help in localization of the position of the electrodes.

The use in human beings of the intracerebral leads we have described has been associated with one untoward event which occurred in a 74-year-old psychotic patient: hemorrhage from the brain.

In a forthcoming paper we shall describe the pathologic findings in a series of 31 dogs in which we investigated the effects of introduction of our depth leads into the brain and the extraction therefrom. The effects thus observed will be compared with the effects produced by the use of another type of lead which has proved safe (Dodge, Holman, Sem-Jacobsen, Bickford and Petersen 1953).

SUMMARY

The various types of electrodes used for intracerebral recordings in human beings have been reviewed.

A multielectrode lead is described which can be introduced into the brain externally to the needle-introducer. It can be used for recordings in the operating room as well as for ''chronic'' implantation (as ''chronic'' is defined herein). Localization of the tip of the electrode in the roentgenograms of the skull is fairly easy.

The authors express appreciation to the Section of Engineering of the Mayo Clinic, and to W. E. Kuchera and C. S. Pollack, Rochester State Hospital, for their collaboration in making the introducers and the electrodes used in this study.

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PRINTED IN CANADA

REWARD DELIVERY SYSTEM FOR CATS [1]

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(Received for publication: May 15, 1958)

For the behavioral training of cats certain features seem desirable in the apparatus used to provide food rewards. It should be simple, inexpensive, compact, and yet rugged and easily maintained. It should be flexible, operable from remote control and should require no special food or food handling. When used in conjunction with recording of brain potentials, it should represent a minimal source of electrical interference. Training, especially in the initial stages, is facilitated if the reward and the manipulanda are presented in close spatial and temporal juxtaposition, and if olfactory and visual food cues are constantly available to the cat. Most currently available reward delivery systems lack some of these features. Frequently, they are complex, expensive and require a great deal of laboratory space. Special foods or food-handling may be necessary, which are time consuming in preparation, difficult to preserve, and which may involve a period of adaptation by the cat.

The reward delivery system described here has many of the desirable characteristics listed above. In contrast to other such systems, it operates by controlling the time during which the cat has access to a whole food ration rather than by dividing the ration into small portions which are periodically presented. A dish of the cat's standard food is placed in a food box with a sliding lid. Holes in the lid permit the cat to see and to smell the food at all times, but he can eat only when the lid is open, so that the amount of reward can be controlled by timing the duration of the lid opening. Levers to operate the lid mechanism are placed on the food box immediately adjacent to the food dish.

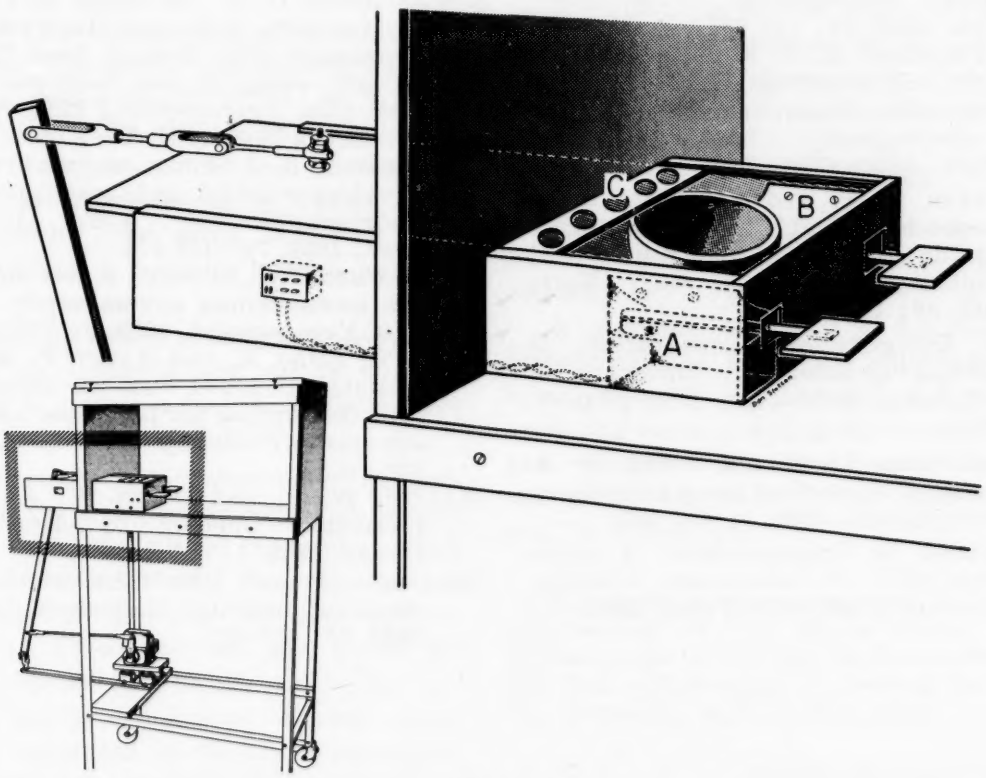

Fig. 1
Training cage with food box and lid activating system.

Figure 1 shows the cage, food box, and the lid-activating system. A dish of the cat's standard food

1 This work was supported by USPHS grant B-611, M-1169 and a grant from the Ford Foundation.

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is placed in the food box. Holes in the sliding lid (C) permit the cat to see and smell the food but he can eat only when the lid is open. The lid-opening mechanism is activated by pedals attached to micro switches (A) with protective covers (B). A pedal-press closes the micro switch which starts the lid opening motor. The motor, obtained for less than 5 dollars from a surplus store, was originally used in an aircraft propeller-pitch controlling system. It operates on 24 V. D.C. An arm on the motor shaft moves back and forth, and relays are provided which permit adjustment of the movement-limits in each direction. Movement of the motor arm is transmitted through a linkage to open and close the food box lid. This linkage, also shown in figure 1, is adjustable by means of turnbuckles at both ends.

In our laboratory, a 24 V. D.C. power supply and a program timer are so arranged that a lever press activates the programmer which opens the lid, leaves it open for an adjustable period of time, and then shuts it. The motor is installed on 4 shock mountings which absorb the linkage torque when the lid meets resistance. This prevents injury to the cat when its head is not withdrawn from the food box as the lid closes. A lever press also activates a holding circuit which deactivates the levers during the lid cycle. Correct and incorrect lever presses are recorded by means of electric counters. The motor case, power cable, and control connections are shielded and grounded to minimize electrical interference when recording from electrodes in the cat's brain during training.

Several cats have been trained in this apparatus using canned cat food in a common feeding dish. In each instance, pedal pressing and subsequent eating responses occurred within the first training session and rapidly became associated to the tone used as conditioned stimulus. Cats quickly learned to withdraw their heads before the lid closed. With the lid-open time adjusted to approximately 4 sec. per trial, cats ordinarily consume approximately 8 ounces of food in 20 to 30 trials over a half-hour training period. The reward system has been used almost daily over a period of 4 months and has functioned reliably, requiring only occasional cleaning. The cage itself is constructed around a rectangular frame which is mounted on swivelling wheels. The vertical members are steel connected by hardwood cross-braces. The floor, two walls and door are masonite panels, screwed to the frame. They are easily removable for cage modifications. The fourth wall is glass to permit observation. The removable lid is of wire mesh to permit light access for observation and photography. The entire cage and lid activation system was constructed at a material cost of less than 40 dollars.

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PRINTED IN CANADA

AUTOMATIC TRANSPORT DEVICE FOR MICROELECTRODES

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(Received for publication: June 3, 1958)

To record action potentials from single cells in the nervous system it is requisite that the microelectrode be advanced through the tissue in steps of a few micra. In addition, the transport system must be extremely stable. We have developed an automatic electrode transport which fulfills these requirements. The device is small and light enough (50 g.) to be mounted directly on a closed fluid-filled chamber cemented on the skull of the experimental animal (Davies 1956). The device has been used in studies of the cortex of the cat. With this set up, the activity of single units has been recorded as long as desired up to at least three hours and single units have proved singularly easy to find.

A reversible two-phase synchronous motor with a phase angle of 90 degrees has been constructed with a small and well balanced rotating mass to reduce vibration. With an alternating current of at least 3 V. r.m.s. the motor turns one revolution per cycle. The diagram (fig. 1, A) shows the magnetized rotor (a) and stators with winding (b).

The motor shaft (s) turns the worm screw (w) via a 5:1 ratio gear (g). The worm wheel (h) is made of nylon and has two internal threads per mm. It drives the hollow steel screw (r) carrying the holder for the microelectrode (e). Rotation of the screw (r) is prevented by the groove (o) into which fits a perspex key (k). One revolution of the motor shaft advances the electrode one micron.

The microelectrode enters the chamber (c) through a rubber packing (p) (fig. 1, B). The microelectrode is fitted into the holder (e) containing a ringer filled cavity (i) surrounded by a layer of perspex insulation (l) and a metal screen (m). The signal is carried to the amplifier by the chlorided silver electrode (t) and the coaxial cable (h).

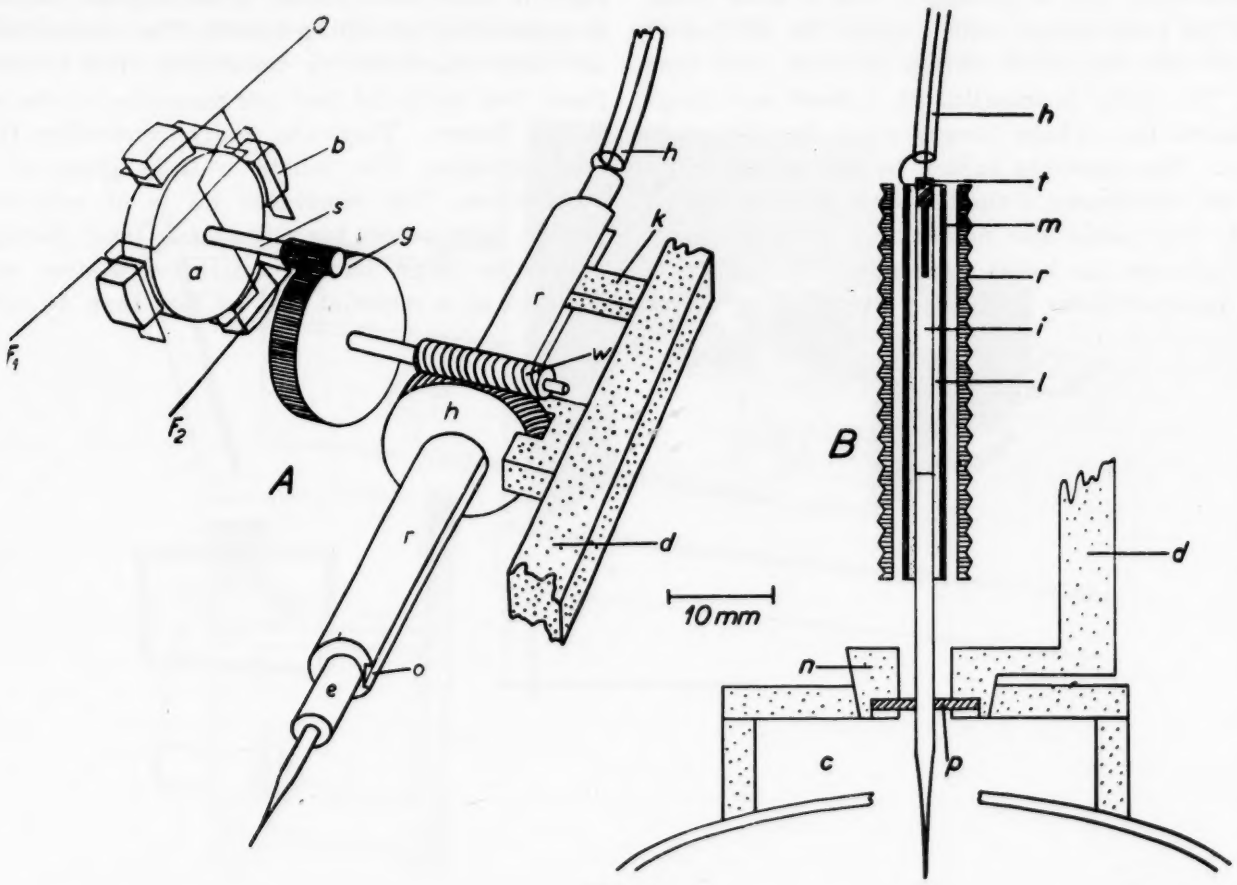

Fig. 1
A. Motor driven device for the transport of microelectrodes. B is a detailed drawing of screw (r) with electrode holder (e) to show the connection of the electrode to the cable (h) and to the chamber (c) and the mounting of the transport device on the chamber via (d). For further explanation see text.

The perspex frame (d) of the device is fitted in the roof of the chamber (c) by means of a cone (n).

The motor is driven by a generator which consists of a power supply, a low frequency oscillator and two power transistors (fig. 2). The oscillator has a frequency range of 0.5 to 50 c/sec. and supplies the signal for the power transistors. One transistor receives a signal with its phase shifted 90 degrees with respect to the signal of the other transistor. To record the distance travelled by the microelectrode, one counter indicates the number of micra travelled by the electrode forward and another indicates movements in the reverse direction.

At present the electrode transport is started and stopped by manual operation of a switch. It is planned to add arrangements for automatic stop of the generator when spike potentials are encountered, by a blocking voltage delivered to the anode of the oscillator by an Eccles-Jordan type trigger circuit (Eccles and Jordan 1919), triggered by the amplifier output. When examination of the responding cell is completed, the oscillator may be released by a push-button.

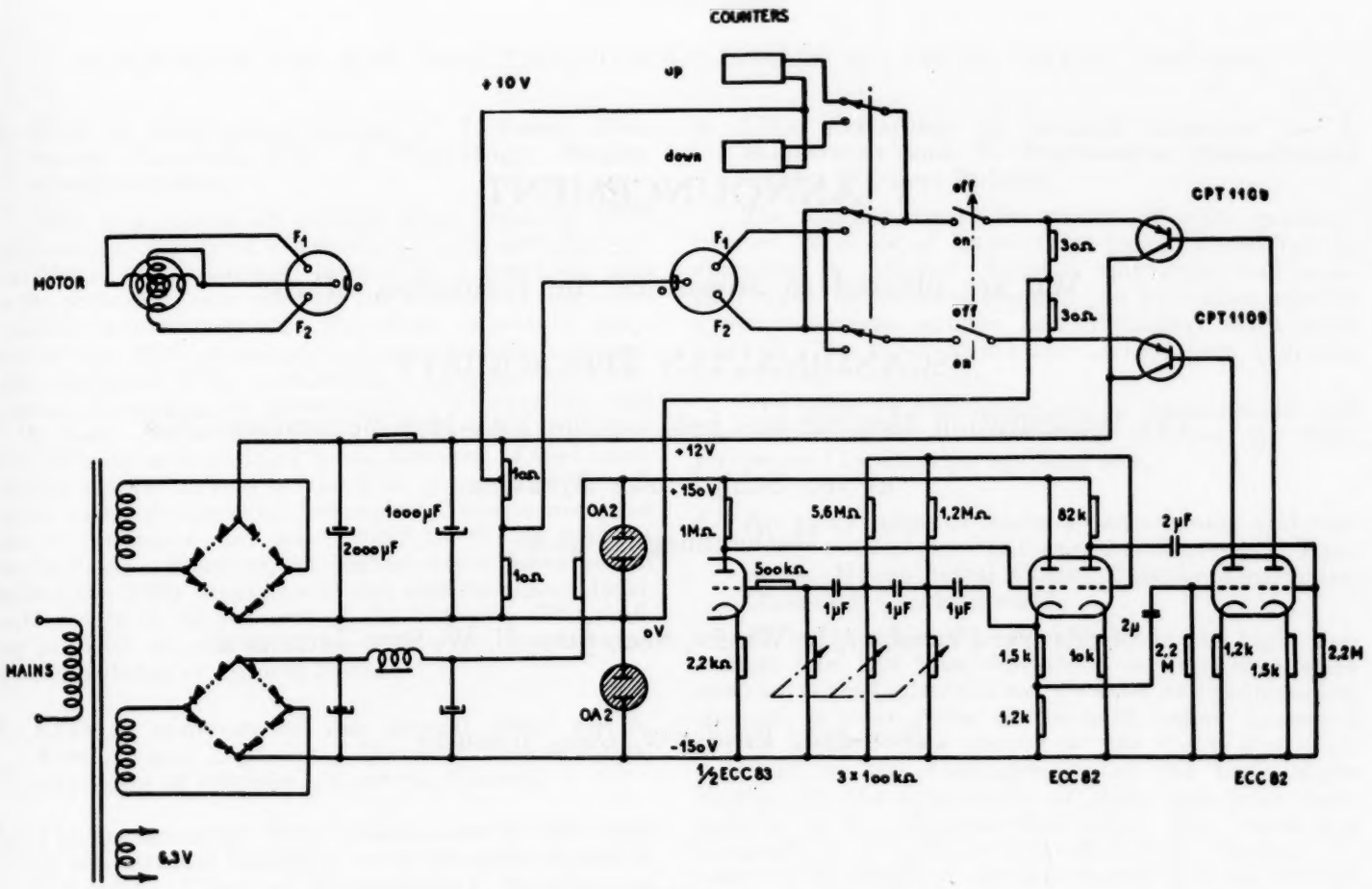

Fig. 2
Diagram of the AC-generator to operate the motor.

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ANNOUNCEMENT

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The Inauguration Meeting was held on the 13th-14th September 1958

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SOCIETY PROCEEDINGS

CZECHOSLOVAK ELECTROENCEPHALOGRAPHIC COMMITTEE OF THE NEUROLOGICAL SOCIETY AND MEETING OF THE POLISH ELECTROENCEPHALOGRAPHERS

Clinic of Neurosurgery, Academy of Medicine, Cracow, Poland

June 19-20, 1958

SYMPOSIUM ON THE ELECTROENCEPHALOGRAM IN FOCAL BRAIN LESIONS

1. EEG of intracranial lesions. — J. Simek, Thomayer Hospital, Div. of Neurology, Prague, Czechoslovakia.

This is a review of modern possibilities of EEG localization. The most exact clinico-electrographic correlation is in hemispheral intracerebral tumours. But in the posterior fossa tumours the EEG can bring some valuable information too. The most important property of the EEG examination is its absolute harmlessness. Repeated EEG examination multiplies its worth. Among the activation methods the overbreathing still is the best. The author, together with Stein, examined 370 patients with verified brain tumours. Exact localization was performed in about 60 per cent of the patients with intracerebral hemispheral neoplasms. The site of the lesion was ascertained in 83 per cent of the patients. However, in extracerebral hemispheral lesions the EEG diagnosis of the site was exact localization only in 35 per cent of the patients. The reading of EEG records must be done with greatest possible knowledge of clinical facts.

2. EEG in tumours of the central area. — A. Kunicki and J. Trabka, Clinic of Neurosurgery, Academy of Medicine, Cracow, Poland.

3. The results of the EEG examination in 200 cases of intracranial tumours. — J. Grabowski and I. Gościński, Clinic of Neurosurgery, Academy of Medicine, Cracow, Poland.

The authors give an account of their experience gained from the observation of 200 cases of intracranial tumours.

EEG disturbances were present in 179 cases (89 per cent) normal EEG in 21 cases (10.5 per cent). A precise localization was obtained in 102 cases (68 per cent), a false localization in 3 cases.

The most precise results were obtained in the tumours of the convexity; in other cases a localization was obtained only in 5 cases of cerebellar tumours.

The possibilities of EEG localization of tumours localized elsewhere than the convexity are restricted; there exists still a possibility of differentiation between the III ventricle and hypophyseal tumours, and between the posterior fossa and supratentorial tumours.

The EEG examination gives no possibility of diagnosing the nature of the tumour. Conclusions may be made only on dimensions of anatomical and functional lesions.

4. EEG alterations in cerebral tumours. — J. Majkowski and T. Pilipowska, Neurological Clinic, Warsaw, Poland.

The authors report the results of EEG examination of 73 cases of intracranial tumours verified by operation or autopsy. Bipolar, monopolar and nasopharyngeal leads were applied. As activation method hyperventilation, apnoea and Pentothal sleep were applied. The observations are divided into 5 groups of different localization.

The value of EEG examination for diagnosis and localization and the correlations between the EEG picture and localization are discussed.

5. An early stage of brain abscess found and correctly proved by EEG examination. — J. Klapetek, Neurological Clinic, Palacky University, Olomouc, Czechoslovakia.

An early stage of brain abscess in the right prefrontal lobe has been described. At the time when contrast examination did not yet show any pathological changes, a clear focus in the said region developed within 5 days. The growth of the focus was characterised by the disintegration of the basic alpha rhythm, by the appearance of theta and later delta activity in the circumscribed area. The focus was bordered by a region of activated alpha rhythm. Already in the stage of the disintegrating basic rhythm it was possible to observe occipitally bilateral episodic slow theta waves. EEG examination which showed a focus homolaterally with a clinical symptomatology (right-sided hemiparesia) was underestimated. Thirty-three days after the first EEG examination the patient died. The autopsy fully confirmed the EEG localization.

6. EEG observations in the alterations of consciousness. — J. Trabka, Clinic of Neurosurgery, Cracow, Poland.

In a case of postoperative observation of subtotally extirped astrocytoma of the left thalamus and the mesencephalic periaqueductal area a correlation was noted between EEG records and clinical states of consciousness. Three different clinical phases were parallel to three different types of EEG changes.

7. The EEG examination and differential diagnosis in cases of so-called cryptogenic epilepsy. — T. Michalski, Sanatorium for Nervous Diseases, Kościan, Poland.

On the basis of serial EEG examinations the author makes the conclusion that the classical petit mal record (spike and wave) is often changing into atypical bursts. At the same time diffuse abnormalities are observed in the background activity. In patients with atypical bursts and insignificantly altered background activity a tendency to permanent dysrhythmia was observed. On the contrary there is a surprising stability of the multiple spike-and-wave type of record.

As shown from clinical observation, the patients with petit mal type of record (first attacks usually in childhood) show often in the course of illness mental deficiency and grand mal attacks are coexistent with petit mal seizures. In 3 from the 5 personal cases an organic brain lesion was demonstrated. In patients with atypical synchronous and symmetrical bursts on minimally altered background activity dementia developed in the course of the years. In pneumoencephalograms alterations were present. These results have led the author to the opinion that in no one of these types of record cryptogenic epilepsy was present. The stability of EEG records and clinical state in the cases with multiple spike-and-wave records seem to indicate that only in these cases true cryptogenic epilepsy is present.

8. Psychiatric symptoms associated with EEG abnormalities in the temporal region. — J. Roubicek, Psychiatric Clinic, University Charles the Fourth at Prague, Czechoslovakia.

The correlates between the EEG tracings and psychic abnormalities have recently assumed new importance. Certain hallucinoses, episodic illusions, states of decrease of initiative (abulia), episodic irritabilities, paraphasic states, involuntary laughter, atypical schizophrenia-like manifestations and impulsive states show characteristic dispersed or focal changes in the EEG. These usually take the form of slow waves occasionally with spikes most often in the temporal or in the temporofrontal regions. If they occur paroxysmally these manifestations may be considered evidence of psychic or psychomotor epilepsy.

Psychopatic states characterised by sudden impulsiveness or aggressiveness also show many temporally localized electrical abnormalities. The temporal region seems to be involved in episodic anxiety, in some psychosomatic conditions and sexual deviations. Certain EEG changes located in the temporal lobes could be evoked or aggravated by emotional activation through experimental stress situations. Fast activity during LSD intoxication was observed not only in the frontal regions but also in the temporal lobes.

9. A case of musicogenic epilepsy. Clinical and EEG study. — A. Piotrowski, Psychoneurological Institute, Warsaw-Pruszków, Poland.

A case of musicogenic epilepsy was observed during the course of 5 years. The psychomotor seizures were always provoked by sentimental songs interpreted by a popular artist. Only female voice, exceptionally lyric tenor had the same activating power. Other music or song did not provoke clinical or subclinical seizures. Good therapeutic clinical and EEG effect was obtained by Mysoline.

Serial EEG records (17) in the course of 5 years, during different treatments and in the non-treated patient, revealed an unstable temporal slow wave focus present sometimes in the left, sometimes in the right hemisphere.

Possible pathophysiological activating mechanisms are discussed in relation to the specificity of the activating agent.

10. Photostimulation in patients with expansive lesions in the brain hemispheres. — B. Drechsler and J. Stein, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

The authors examined 37 patients with anatomically verified expansive lesions of the brain hemispheres.

The most marked finding in photostimulation was asymmetry in photic driving response in the affected and the healthy hemisphere. On the side of the lesion slow stimulation rhythms produced driving while fast rhythms were reproduced on the healthy side. Changes due to photostimulation were fairly frequently absent from the EEG tracings altogether. An observation of interest was the inhibition of alpha activity by certain frequencies only, mainly low frequencies. Another interesting point was the appearance of harmonic frequencies which were found much more frequently on the sound side, and exclusively on this side in higher frequencies.

Comparison with the results obtained by the thiopenthal test makes quite clear the entirely different mechanism of these two methods of activation.

The interpretation of the results is today very difficult: for the present the authors content themselves with stating that the results of photostimulation can confirm localization revealed by routine EEG examination.

11. Activation methods in EEG. — J. Majkowski and I. Hausmanowa-Petrusewicz, Neurological Clinic, Warsaw.

A review of different activation methods (physical, biochemical and mixed) is given and their usefulness discussed. Different combinations in organic and functional lesions of the central nervous system are discussed, especially in various types of epilepsy. The medico-legal value of activation methods is accentuated. Personal observations were made with hyperventilation, apnoea, Cardiazol, sleep, flicker, insulin and alcohol.

12. Control of the value of activation of the EEG with compression of the carotids in 150 patients. — Z. Mensiková and O. Polák, Plzen Neurologic Clinic of the Charles University, Plzen, Czechoslovakia.

The authors controlled the results of their former paper concerning the value of activating the EEG by compression of the carotids in 150 patients suffering from brain tumours, by acute vascular brain accidents and other diseases. They state that this method always helps the diagnosis of thrombose of the carotids and that it very often helps that of other vascular accidents. In cases of subarachnoid bleeding this method sometimes helps lateralizing the origin of bleeding. The compression of the carotids is of special value in occipito-parieto-temporal tumours. Negative results of the experiments are diagnostic in pseudotumourous syndromes. Accompanying clinical features, if any, are of no importance and in thromboses of the carotids they may even help to diagnose the pathological condition.

13. The value of chlorpromazine as activating EEG method in cases of epilepsy. — H. Ekiert and B. Bigo, Psychoneurological Institute, Warsaw-Pruszków, Poland.

In 23 patients (16 grand mal cases, 3 psychomotor seizures, 4 petit mal cases) a routine EEG examination was compared with EEG records after intramuscular injection of 25 mg. of chlorpromazine. In two cases only after chlorpromazine provocation paroxysmal bursts of delta and theta waves and wave-spike complexes were observed; in these cases, however, other activation methods (hyperventilation, flicker) had previously been applied without result.

In the majority of the patients with normal routine EEG record only slight changes, similar to those described in normal subjects were present after the chlorpromazine activation. In pathological EEG records chlorpromazine provoked an accentuation of the abnormality. Among 6 patients with no alterations in the EEG after chlorpromazine administration, there was not one with petit mal epilepsy.

As the paroxysmal EEG alterations were observed in petit mal epilepsy, special care should be taken in the use of chlorpromazine in such cases.

No correlation was observed between EEG alterations and blood pressure oscillations.

SYMPOSIUM ON THE EEG OF CONDITIONING

1. Bioelectrical aspect of neurophysiological mechanisms in conditioned reflexes. — A. Jus and C. Jus, Psychoneurological Institute, Warsaw-Pruszków and Psychiatric Clinic, Academy of Medicine, Warsaw, Poland.

EEG studies of conditioning in animal experience and clinical observation in man led to:

(*a*) some general theoretic formulas on bioelectric-neurophysiological correlates (bioelectric equivalents of the processes of excitation and inhibition, principle of "relative" evaluation, spatio-temporal analysis of bioelectric mechanisms of conditioned reflexes, "pathways" of temporary connexions, etc.);

(*b*) accumulated clinical experimental observations and replaced general theoretic interpretations by pathogenetic hypotheses (study of EEG structure and reactivity in some states of motor inhibition, e.g. catatonic stupor, narcolepsy, sleep paralysis, phenomena of EEG, EMG-motor dissociation, etc.);

(*c*) suggested EEG studies of some psychic phenomena until bioelectrically unexplored, well analysed in phenomenology but only hypothetically evaluated by the general conditioned reflex theory.

The questions referred to in (*a*) and (*b*) were discussed by the authors in former publications, here a general outline of personal experience in (*c*) will be given.

During the formation of conditioned reflexes bioelectric changes may be observed in specific afferent pathways and in the unspecific brain stem reticular formation and cortical areas. These changes are due to the transformation of the biological value of the conditioned stimulus. Some of these changes are present *before* the other *during* and *after* conditioning.

Bioelectric changes in specific evoked potentials and in the general arousal reaction *before* the conditioning, are related to the extinction of the orientation reflex (habituation) of the conditioned stimulus. Phasic and tonic arousal reaction may be differentiated during partial extinction and chlorpromazine blocking of the brain stem reticular formation.

A voltage increase of evoked potentials and correspondent changes in the arousal reaction are present *during* the conditioning. At the same time a characteristic shift in the topography of blocking reaction is observed (the reaction in the unconditioned stimulus cortical area is shifting to CS area).

After the establishment of conditioning the stability of bioelectric conditioned reaction depends upon the existence of "biologically important" stimulus. In the absence of such a stimulus extinction of the reaction is observed.

The application of a new and strong stimulus (external inhibitor) during the application of an exteroceptive stimulus is provoking reactivity changes in the EEG, which may be evaluated as the bioelectric correlate of attention. The presence or absence of bioelectric reaction is not directly correlated to the human perception.

In the permanently altering reactivity of the CNS some bioelectric reactions to threshold stimuli may behave like reactions to presensoric stimuli.

2. EEG manifestations of the unconditioned and conditioned skin galvanic response. A contribution to the study of the reticular system in man by cutaneous nociceptive activation of the EEG. — J. Holubář, Czechoslovakian Academy of Science, Prague, Czechoslovakia.

In 15 healthy men the skin galvanic responses (SGR) were elicited by electric stimulation of one hand and recorded from the other hand simultaneously with 7 EEG leads. In 191 sessions the stimuli were repeated at regular 30 sec. intervals and thus conditioned reflexes to time were worked out. Three kinds of EEG changes accompanying SGR were found: SGR on the head, generalized K wave or K complex and generalized change of the EEG pattern. In the common cold and similar conditions both responses, cutaneous, and cerebral, were absent. In drowsiness the SGR was abolished, the stimuli were not perceived, but the generalized K waves were present. Similarly, both responses were found if the stimuli were applied at regular 30 sec. intervals, whereas, within these periods the EEG responses only could be elicited. Thus, in transitory periods of conditioned inhibition, even the unconditioned SGR was extinguished.

In 90 per cent of subjects the conditioned SGR to time was worked out. About 100 or more reinforcements were necessary to establish the reflex firmly. The EEG changes accompanying the conditioned SGR were the same as those of the unconditioned SGR. Especially the finding of conditioned K wave is emphasized, since, owing to the non-specific appearance of the K wave to any kind of stimulation, only its conditioning to time is conclusive. This finding is considered as additional evidence of the formation of conditioned reflexes in the brain stem reticular system.

The result has been discussed in terms of the possibility of investigation of the reticular system in

man by the simple method of cutaneous nociceptive EEG activation.

3. Studies on photic driving conditioning in man. — A. Jus and C. Jus, Psychoneurological Institute, Warsaw-Pruszków and Psychiatric Clinic, Academy of Medicine, Warsaw, Poland.

Different types of reactions to rhythmic intermittent light are present in different types of EEG records.

The electrocortical conditioned response in man is as a rule frequency unspecific. Different types of this conditioned response depend upon the actual cortical tonus (simple alpha blocking, arousal alpha activity on a beta background activity). In very rare cases a frequency specific conditioned reaction may be observed in man. In the experimental animal the following stages of establishment of conditioned reaction to rhythmic photic stimulus are observed: general desynchronization, localized frequency specific reaction, localized desynchronization. The instability of the second stage observed in the animal experiment and the rapid formation of retardation in man seem to be the reasons of general absence of the frequency specific conditioned reaction to rhythmic photic stimulus in man.

4. The influence of kinesthetic stimuli on conditioned cortical rhythms in EEG and EMG examinations in rabbit. — J. Majkowski, Neurological Clinic, Warsaw, Poland.

The author discusses the reasons of appearance (in the I, II, III stage) and disappearance (in the III and IV stage) of cortical driving in the rabbit during the conditioned motor reflex. In experiments on rabbits:

(*a*) the extremity involved in conditioned motor reflex was paralysed by curare; in this period of paralysis a typical conditioned reflex could be obtained;

(*b*) in the period of paralysis rhythmical passive movements of this extremity were performed during the operation of CS;

(*c*) 1 per cent pantocain was administered into joints of this extremity;

(*d*) unconditioned motor reflexes were registered.

An EEG and EMG analysis of the mentioned experiments led the author to following conclusions:

(1) isometric tonus has different afferent pathways and cortical receiving areas than isotonic tonus;

(2) in the process of motor conditioning the influence of kinesthetic stimuli plays an important role in the appearance of the conditioned motor reflex;

(3) the appearance of driving in the kinesthetic analyser is the expression of the conditioning of kinesthetic stimuli;

(4) the disappearance of driving (desynchronization) — in the performed reflex — is provoked by unconditioned excitation of sensory cells of the motor cortex by kinesthetic stimuli.

FREE COMMUNICATIONS

1. EEG observations in microcephaly. — W. Horyd, Neurological Clinic, Academy of Medicine, Gdansk, Poland.

A 7 year-old microcephalic child with high degree of hypoplasia of cerebral tissue was submitted to serial EEG examinations. The child was always keeping the same position, laying in bed with his head turned back, upper and lower extremities in flexion. No voluntary movements, only primitive unconditioned activity was present. This was stationary during the 7 year observation. The EEG records registered during this 7 years' period remained unchanged: a polimorphic slow activity and no reactivity to stimuli was recorded in all serial EEG records.

2. The influence of sonic stimulation of a constant tone of different frequencies on human electroencephalogram especially in children. — I. Lesný and J. Odvárková, Children Div., Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

The influence of sonic stimulation with the constant tone on the electroencephalogram was examined in 75 persons, 67 children and 8 adults. The frequencies were 1700 c/sec. 1400 c/sec. 1100 c/sec. 900 c/sec. 680 c/sec. 450 c/sec. and 200 c/sec. The strength of the tone was 100 decibels and the duration of the application was 15 sec. The reaction of the electroencephalogram on the sonic stimulation was variable. The most common types of reaction were decrease in amplitude, increase in amplitude, shift to the slow side of the frequency spectrum and epileptic discharges. It was ascertained that the EEG changes varied with different pitches of the tone. The decrease of amplitude of the slow wave was observed more with high pitched tones, the decrease of amplitude of the alpha rhythms was more frequent in the middle tones. The shift to the slow side was more in the extreme tones than in the middle ones. Epileptic discharges appeared in a third, part of the cases had fits, the discharges were always generalized, never focal. The most interesting result of this examination is in the demonstration that the EEG reaction to sonic stimulation changes with age. The changes were greater in the age groups of 6-10 and 10-15 than in the age groups of 0-3, 3-6 and in the adults.

3. EEG records in paroxysmal periodic abdominal pains in children. — A. Koślacz-Folga, Institute of Mother and Child, Warsaw, Poland.

Serial EEG examinations were carried out in 44 children, aged from 3-13, with periodic abdominal pains, generally accompanied by vegetative disorders and in a few cases by twitches and by disturbances of consciousness. No alterations from the clinical point of view were observed in the abdomen. Pathological alterations mostly paroxysmal were present in 2/3 of the EEG records. This seems to indicate the existence of an intimate relationship with CNS disturbances and epilepsy.

The practical importance of EEG examination in differential clinical diagnosis is emphasized.

4. EEG research on pathogenetic differentiation between migraine and vasomotor headache. — T. Domzal, Neurol. Div. of the Central Military Clinical Hospital in Lodz, Poland.

EEG examinations were carried out in 60 patients with headaches of vascular origin (30 with vasomotor headaches and 30 with migraine).

In the first group low voltage activity with dominant beta and some sporadic theta waves in unipolar leads was observed. Only in 3 cases of this group distinct pathological EEG alterations were present.

In the second group, i.e. in migraine, a high voltage activity with abundant, irregular, often asynchronic sharp peak alpha was present. In 15 cases distinct pathological alterations (in 6 diffuse, in 7 unilateral) were present. In 6 cases paroxysmal, short bursts of irregular high voltage sharp waves, theta and delta activity, were observed. All these alterations were present in the inter-seizure period and were independent from the length of the illness and frequency of attacks.

These results have led the author to the conclusion, that in both forms of headaches of vascular origin, a different pathogenesis is present although the pain is always of vascular origin.

The vasomotor pains are the expression of chronic angiospastic states, originating on the base of a labile and ''feeble'' nervous system. The alterations in migraine seem to be on the contrary due to some alterations in the diencephalon, provoking the above described EEG pathology. This hypothesis seems to be justified by the following facts: (*a*) the presence of EEG alterations independently from the length of the illness; (*b*) the presence of alterations as frequently in the period between attacks as during the attack, (*c*) frequent discrepancy between the localization of the pain and the EEG alterations, (*d*) presence of paroxysmal alterations and (*e*) good effects of anticonvulsive therapy.

5. EEG studies of a large series of cases of narcolepsy and hypersomnia. — B. Roth, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

The author analysed 432 tracings of 225 cases of narcolepsy and hypersomnia. He draws the following conclusions: narcoleptic paroxysms show a characteristic sleep activity in the EEG. Cataleptic paroxysms as well as states of sleep paralysis are in the majority of cases accompanied by sleep activity, but in some cases the tracing remains normal. In the intervals between paroxysms infraclinical signs of sleep activity can be found, alternating with normal activity. In idiopathic narcolepsy there are no signs of pathological rhythms, in symptomatic narcolepsy frequent signs of pathological activity are found in addition to sleep activity. Hypersomnia is also characterised by alternating normal and sleep activity. In organic cases of hypersomnia pathological changes are found, whereas in functional cases there is no pathological activity with the exception of an exaggerated reaction to hyperventilation which is frequently found and which may be accompanied by signs of hyperventilation tetany. Deep breathing, activation by Cardiazol and benzedrine normalizes the tracing if preceded by sleep activity.

6. Sleep activity in the EEG as a manifestation of chronic insufficiency of wakefulness. — B. Roth, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

The author studies the period between complete wakefulness and established sleep and divides it into 4 electroencephalographically distinct phases, each of them characterised by a typically changed reactivity to external stimuli. Further the normalizing effect of methods of activation on the recorded sleep activity is described. In the second part of the paper the conditions in which clinical or infraclinical signs of sleep activity occurred are listed. They include mainly narcolepsy and hypersomnia, organic conditions of the mesodiencephalic region (esp. traumatic, encephalitic etc.) and finally neuroses and pseudoneuroses. In neurosis signs of sleep activity have been found in 65 per cent of all tracings. In the author's view this is evidence of chronic insufficiency of wakefulness as a consequence of insufficient nonspecific afferent inflow to the cortex due to a functional insufficiency of the reticular activating system of the brain stem. The author believes that not only the EEG signs of sleep activity, frequently accompanied by real hypersomnia, but also the neurotic symptoms themselves are connected with this mechanism.

7. EEG examinations in the course of paranoid schizophrenia treatment by chlorpromazine and Serpasil. — H. Ekiert and B. Bigo, Psychoneurological Institute, Warsaw-Pruszków, Poland.

Serial EEG examinations were carried out in 54 patients, 36 treated by chlorpromazine, 18 by Serpasil before, during (every 7 days) and after treatment (every month) when still on sustaining doses until the normalization of the EEG.

A certain number of these patients was treated by chlorpromazine first and by Serpasil subsequently, because they were without improvement on one of the treatments.

The following conclusions could be made:

(1) During the treatment with chlorpromazine or Serpasil in comparison with the EEG before treatment there was observed either (*a*) an absence of EEG changes, or (*b*) a slowing of the activity, or (*c*) a dominant fast activity with few sporadic slow waves.

(2) The slowing of activity, which the authors consider to be the expression of diminished cerebral tonus, was usually observed in periods of psychic improvement during the treatment.

(3) Parallel with this slowing a diminished reactivity for auditory and visual stimuli was observed.

(4) The persistence of slow activity during treatment was usually correlated with deeper and more stabile improvement.

(5) Only few EEG, without slow activity or with only sporadic slow waves and dominant fast activity were usually present in patients with no improvement.

8. The effect of Largactil on the EEG response (evoked potential) to the light stimulus in man. — L. Cigánek, Neurological Clinic, Bratislava, Czechoslovakia.

The responses to the flash of a stroboscope (evoked potentials) picked up by scalp electrodes over the occipital area were recorded by the superimposition technique described by Dawson. The first three waves of this response have characteristics (localization, latency, maximum frequency-resistance) compatible with the assumption that they represent the primary, specific response. Under Largactil medication typical symptoms were observed (inhibition of psychomotor activity, desinterestedness and light sleep). In spite of all this state the responses to the flash remained

unchanged, although there were often signs of sleep in the EEG tracings. The amplitude of the artefact produced by the blink component of the muscular startle reaction was reduced after Largactil. The results permit the conclusions that Largactil has no effect on the specific visual afferent system and are supporting the hypothesis that Largactil has a preferential effect on the reticular activating system.

9. EEG examinations in chronic professional intoxication by carbon disulphite. — W. Królikowska and Z. Rucińska, Neurological Clinic, Lodz, Poland.

EEG records and neurological examination of 96 workmen of the Artifical Fibre Factory utilizing CS_2 in the cycle of production was carried out. The patients were working in sections where the CS_2 concentration was high and in some periods exceeded 10 times the so-called ''safety limit''. The patients were in the age of 24-63, and their work time in these factory sections was in 15 cases between 5 and 10 years, and in 81 cases more than 10 years.

Clinical examination revealed different neurological symptoms, which can be divided into three syndromes: neurosis, polyneuritis and encephalopathy (subjective complaints and organic lesions of the CNS). Very often in one patient a combination of these syndromes was observed.

In 43 cases the EEG was normal; in 36 — very low voltage activity with few low voltage (10-20 μV.) alpha waves was present; in three cases only of this group of 36 beta activity could be identified by visual analysis. In 17 cases pathological alterations, mostly diffuse theta waves were present. In 3 cases of the last group alterations appeared paroxismally.

No correlation was observed between the clinical form of intoxication, its gravity and the EEG record. Very characteristic was, however, the high percentage of low voltage activity (45.5 per cent) in comparison with 15 per cent in groups of normal persons.

These results are concordant with the results obtained by Cesare and Salvini (1953) and Montanini (1956) in 10 and 14 cases.

10. The origin of delta waves in EEG. — Jiří Stein, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

This is an analysis of more than 600 patients with intracranial lesions; 370 of them were verified. The author was mostly concerned with slow, delta, waves. On the basis of his findings and on the data reported in the literature he came to the following conclusions:

(1) alpha rhythm represents the normal electrical activity of the cortex only in correlation with other parts of the central nervous system, the deep and superficial cortical structures. It is influenced by the ascending reticular system;

(2) delta rhythm is the original electrical activity of the isolated cortex. It appears when the cortex is isolated from the influence of other parts of the central nervous system as it happens in many pathological and in some physiological circumstances;

(3) in deep lesions of the central nervous system the delta waves appear, on the other hand, in the direct lesion of the cortex the alpha rhythm increases in amplitude;

(4) the place of the most frequent appearance of delta waves are the frontal regions. This is because the tracts leading to them are very easily alterated;

(5) the focus of the pathological slow activity does not correspond to the direct localization of the pathological process, but to its cortical projection. The difference between the EEG changes in the deep parts of the cerebral hemispheres and the pathological focus in the brain stem or posterior fossa is only in the localization of the slow waves, not in their type. Only in the lesions of cortex is the type of the record changed.

11. Some remarks on the EEG findings in diabetes. — W. Królikowska, H. Lisiecka-Adamska and A. Prusiński, Neurological Clinic, Lodz, Poland.

EEG examinations were carried out on 50 diabetic patients (in the age of 27-70) with different length of illness. Neurological, ophtalmological and oscillometric examinations were carried out in all cases.

In about 50 per cent of cases distinct EEG abnormalities were present, and this mostly in patients with symptoms of encephalopathy. Further investigations on correlation between EEG and vascular changes in different organs are intended.

12. EEG after novocainisation of the frontal thalamic pathways in patients suffering from intractable pains. — Z. Mensiková and O. Ledinský, Plzen Neurologic and First Surgical Clinics of the Charles University, Plzen, Czechoslovakia.

In seven patients suffering from intractable pain, the fronto-thalamic pathways were injected with novocain by the authors, who, at the same time, studied the electroencephalographic alterations caused by this procedure. They observed both focal occurrence of slow waves in the frontal regions, and irritations at the posterior borders of the foci, as well as some fine synchronous rhythms. More marked alterations were found in those patients, in whom they had succeeded to calm the pain with novocain. After comparing the different descriptions reported in the literature the authors state that novocainisation of the fronto-thalamic pathways causes less disturbances of the electric activity than frontal lobotomy and further that there is no danger that there might develop alteration of personality, or arise posttraumatic epilepsy.

13. EEG alterations in abortive repeated anaphylactic shocks. — J. Narebski, Department of Neurophysiology and Comparative Physiology at the Nicholas Copernicus University in Torun, Poland.

From 4.5 to 7.5 ml. of horse serum was injected i.v. every 6-10 days to 13 rabbits. Every rabbit received during the 80 days' experimental cycle 62-72 ml. of horse serum (Arthus, Hurynowicz, Czarnecki, Bagiński). In the majority of animals a few days before serum injections a control injection of 7-8 ml. 0.9 per cent NaCl was done with the same rapidity as serum injections.

Every horse serum injection in the above mentioned doses (with the exception of the first sensibilizing injection) produced in the rabbit a state called ''abortive anaphylactic shock''.

Unipolar EEG records with indifferent electrode on the ear were recorded by means of contact electrodes every 6-10 days, before and immediately after the end of horse serum injection, and also every 5-7 min. during an hour after the injection. In the majority of experiments the EEG was recorded also during the injection.

Results.

Intravenous injection of about 10 ml. of 0.9 per cent NaCl during 2-4 min. does not alter the EEG.

The first sensibilizing horse serum injection does only minimally alter the EEG record or not at all.

The repeated injections beginning from the second one, are provoking still more distinct alterations in the EEG, which sometimes are very prominent. The most prominent alterations are appearing during and immediately after the end of the intravenous injection. They are ushered in by a voltage increase during the injection, reaching its peak at the end of the injection and then dropping gradually in 5-30 min. to the original level. This voltage increase is observed only in the fast activity. A gradual voltage increase was observed from one injection to the other.

Conclusions.

The EEG alterations are evaluated as an expression of cerebral cortical involvement in specific shock reactions of the anaphylactic type.

14. EEG study of 42 cases of hypocalcemic tetany. — B. Roth and O. Nevsimal, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

The authors studied 42 patients with hypocalcemic tetany; 29 of them showed signs of cerebral involvement (epilepsy, psychosis, neurosis, etc.). Seventy-seven EEG tracings were made, 66 recordings were considered pathological, showing a generalized theta activity, less frequently episodes of theta waves or a predominance of rapid activity. The hyperventilation response was very prominent in most cases, showing in the majority of cases hypersynchronous slow waves. The severity of clinical and EEG signs were, on the whole, correlated. The recovery due to appropriate treatment, was followed by normalization of the tracings. In the author's opinion the EEG changes are due to hypocalcemia, which is acting by raising the excitability of a synchronizing mechanisms of the brain stem as well as by producing changes of cellular permeability in the brain.

15. EEG studies of 89 cases of normocalcemic tetany. — O. Nevsimal and B. Roth, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

In 89 patients with normocalcemic tetany 163 EEG recordings were made; 82.4 per cent of the recordings were considered pathological. In 65 per cent of all tracings signs of infraclinical sleep activity were found. Other spontaneous abnormalities were noted in 17 per cent of the tracings (generalized or episodic theta activity). Overbreathing provoked pathological changes in 134 recordings, in the majority of cases hypersynchronous delta waves. The intensity of the EEG changes is in keeping with the individual sensibility to overbreathing, tested by a special hyperventilation test. In the author's opinion these observations should be interpreted as a proof of the participation of the central nervous system in the mechanism of tetanic spasms which is considered to be integrated by the mesodiencephalic reticular system.

16. EEG alterations in the course of meprobomate treatment. — S. Leder and Z. Paśniczek-Gogolowa, Psychoneurological Institute, Warsaw-Pruszków, Poland.

Twenty-three patients (14 with neurasthenic neurosis, 7 with hysteric neurosis and 2 psychopaths) were examined during the course of meprobomate treatment. In 5 patients coexisting organic lesions (platybasia, hypertension with general arteriosclerosis, hyperthyreosis, hypertension, Morgagni-Stewart-Morel syndrome) were present. In every case EEG was registered before the treatment, after one meprobomate provocation (35-70 min. after oral administration of 0.4 meprobomate) and after the end of a 3-6 weeks of meprobomate treatment.

Only in 5 patients was the pre-treatment EEG normal, in other patients theta or delta waves or fast activity intermingled with the background alpha activity was present. Alpha blocking to visual stimuli was present in the majority of cases.

No correlation was established between the EEG changes and clinical state. However, in organic cases a dominant beta was registered.

After one provocation (oral administration of 0.4 meprobomate) in the majority of patients an increase in the voltage and quantity of the alpha activity, a decrease of alpha frequency and an increase of theta and delta activity was observed. In a few cases no alterations were present. In one a decrease of dysrhythmia and a disappearance of theta activity was observed. In records with dominant beta activity these changes were more frequent.

After the treatment in some cases a slowing and increase voltage of the alpha activity was seen, in others decrease of theta and appearing of fast activity or decrease in voltage and some increase in frequency.

No correlation was established between the EEG record after the provocation and the terminal record and/or clinical results of the treatment, nor between the first EEG and the results of treatment.

It was established that in all patients with no improvement the EEG remained unaltered, and in the majority of clinically improved patients the records showed a tendency to slowing and voltage increase.

Control records were made in 7 normal adults.

17. EEG examination in Friedreichs ataxia and neural amyotrophy. — I. Lesný and V. Vojta, Neurological Clinic of the University Charles the Fourth at Prague, Czechoslovakia.

In 22 children suffering from Friedreichs ataxia and neural amyotrophy an EEG examination was performed. In 13 of them (7 cases of neural amyotrophy and 6 cases of Friedreichs ataxia) there was an EEG abnormality, which presented itself in bilaterally synchronous discharges of slow waves 3-5 c/sec. Only in one of these 13 cases there was a positive history of fits.

PRINTED IN CANADA

JOINT MEETING OF THE CENTRAL EEG SOCIETY WITH THE EASTERN EEG SOCIETY

New Lecture Theatre, Toronto General Hospital

Secretary: J. W. SCOTT
Toronto General Hospital, Toronto, Ont.

September 12-13, 1958

1. Evaluation of fronto-parietal notched-wave activity. — J. C. METTS, JR. and J. S. GARVIN, Chicago, Ill.

An easily recognized wave form which we have termed ''notched-waves'' occurs in the fronto-parietal areas during sleep. This complex appears to be a slower higher voltage wave with a normal spindle frequency over-lying. At times one sees transition forms and a definite spike and wave formation may occur. A review of 500 records previously interpreted as normal awake and asleep revealed 3 per cent to show this wave form.

A review of 100 records which show this abnormality alone and another 100 which show additional abnormality has been carried out. There is essentially no difference in sex incidence. Forty-three per cent of the cases occurred between ages 11 and 30. Twenty-five per cent of the cases had a history of trauma. Only 2 patients had neoplasms and these were meningiomas.

Nine patients with only ''notched-waves'' had definite grand mal seizures while another 38 had ''black-outs'', faints, or syncope. Patients with both ''notched-waves'' and other abnormality had a much higher incidence of grand mal convulsions. Headache was a frequent symptom occurring in 31 patients. The most common additional abnormality seen in records with ''notched-waves'' consisted of 14 and 6 per sec. positive spikes, small sharp spikes and atypical spike and wave formations.

The response of symptoms to anticonvulsant medication has been encouraging.

2. Electroencephalographic changes in acute brain-stem vascular lesions. — W. J. FRIEDLANDER, Boston, Mass.

It has been well established that destructive lesions anywhere from the diencephalon rostrally may produce alterations in the EEG and that probably lesions of the spinal cord do not effect the EEG. However, there has been but little clinical or experimental investigation into the EEG changes associated with destructive, non-tumorous lesions of the intervening brain-stem although it has been apparently assumed that such lesions do not cause much if any change in the EEG. Particularly because of the recent interest in basilar artery insufficiency, it would be of value to determine what indeed does happen to the EEG in acute brain-stem vascular lesions.

The EEG's of 31 patients were reviewed; these were cases with thrombotic or embolic lesions in the mesencephalon and/or pons and/or medulla in whom there was no evidence of similar lesions elsewhere in the brain nor other serious brain disease that of itself could have produced EEG changes. All diagnoses were based on clinical findings.

Nine patients had abnormal EEG's, 2 had borderline EEG's and the rest were interpreted as normal. The most outstanding finding was that when there were EEG changes they were only of a minor or mild degree. There was nothing specific about the type or the location of the abnormalities. Various special techniques e.g., light stimulation, Metrazol-activation, and sleep were used in some cases but they may not have added any further significant information.

It is concluded that an abnormal EEG regardless of the type or the location of the abnormality, is not inconsistent with a clinical diagnosis of an acute brain-stem vascular lesion provided the degree of abnormality is not greater than mild.

3. Electroencephalographic findings in ex-premature infants with partial and complete blindness due to retrolental fibroplasia. — D. R. METCALF, Denver, Colorado.

As part of an intensive, multidisciplinary follow-up study of premature infants, electroencephalograms have been obtained on 30 blind and partially blind children with retrolental fibroplasia. Subjects were all under 1500 g. birth weight, were born in 1949 and 1950, and were cared for in the University of Colorado Medical Center Premature Infant Nursery.

Detailed information is available regarding course in the premature nursery, subsequent medical history, growth and development, and performance on psychological tests.

Abnormal electroencephalograms have been obtained on 90 per cent of the subjects. Presence of abnormality does not relate to intelligence, and relates only indirectly to the existence of disorders such as epilepsy, spastic diplegia, or severe mental retardation. A positive invariant relationship is found between blindness and EEG abnormality.

The EEG abnormalities are of many varieties, but there is an unusually high incidence of focal disturbance. Focal involvement is generally maximal over the occipital areas, and occasionally this is the only abnormality.

Hypotheses under investigation are discussed. Slides are used to summarize the data and present sample EEG's.

4. Some electrical responses of the eye and optic lobe of the chick embryo to photostimulation. — J. J. PETERS, A. R. VONDERAHE and T. H. POWERS, Cincinnati, Ohio.

Both newly hatched chicks and chick embryos were examined for electrical changes of the eye and optic lobes in response to photostimulation up to frequencies of 60 flashes per sec. In newly hatched chicks both the stimulated eye and the contralateral optic lobe manifested the ''on'' and ''off'' effect as well as individual electrical changes in response to each flash of light up to frequencies of 40 per sec. At 18 days of incubation (stage 44, Hamburger and

Hamilton) electrical responses of chick embryos to photostimulation may be absent at the outset of the experiment. However, a definite, though sometimes inconsistent electrical change, can be evoked after several minutes of photostimulation. At this age of 18 days the eye and optic lobe of the embryo yield the largest amplitude of electrical response when subjected to photostimulation at frequencies of 4 to 12 per sec. Electrical recording from the eye and optic lobes of chick embryos of 16 days (stage 42) and earlier stages showed no electrical change in response to photostimulation.

5. A study of the occipital alpha potentials in organic brain lesions. — Francis J. Millen, Milwaukee, Wis. and Reginald Bickford, Rochester, Minn.

One hundred electroencephalograms were reviewed representing 92 cases of mixed organic brain lesions of a focal type. Of these, 72 cases were brain tumors, 12 degenerating brain, 4 brain abscess, one vascular lesion and 3 cases where the nature of the lesion was undetermined. Six clinical cases represented serial electroencephalography. The routine electroencephalogram was reviewed in its entirety by the visual analysis method and particular attention was paid to comparing the activity recorded from the occipital and posterior parietal electrodes placed over homologous points of the scalp overlying the occipital cortex. The alpha activity recorded by these electrodes represent the occipital alpha rhythms. In all but 3 of the 92 cases the nature and location of the lesion was determined by necropsy, direct surgical examination, or by other acceptable techniques. All significant clinical and laboratory data in each case was carefully compiled in arriving at the results and observations.

The occipital alpha activity was studied as to its per cent time, its dominant frequency rate, its dominant voltage amplitude and its frequency variation. Asymmetry was determined by comparing these characteristics on the two sides. These data were chartered against the nature, size and location of the lesion, the presence or absence of hemianopsia, the presence or absence of increased intracranial pressure, and the degree of delta and theta activity present in the entire record as well as in the occipital areas.

The following observations were made. the occipital alpha rhythm on the side of the lesion was usually less well defined; its per cent time was lower; considerable frequency variation in the alpha rates was present; the dominant alpha frequencies were in the slower ranges; the dominant alpha voltage amplitude was lower and in general the alpha activity was more irregular and unstable appearing. Occasionally the occipital alpha amplitude was higher in voltage on the side of the lesion than on the opposite side. The per cent time of alpha present was less as the per cent time delta activity was greater in the area. The per cent time alpha activity was less as increased intracranial pressure was present. In all cases studied, localizing or lateralizing alpha asymmetry was present in 55 per cent, absent in 41 per cent, and on the side opposite of the lesion in 4 per cent. When hemianopsia was present lateralizing alpha asymmetry was present in 73.6 per cent. When hemianopsia was absent or undetermined asymmetry was present in 30 per cent of the cases. The presence of asymmetry or distortion in the occipital alpha rhythms was most constant on the side of the lesion. Although asymmetry was present most constantly when the lesion was near to or directly involved the occipital lobe itself, or its subcortical optic nerve pathways, it was also present in lesions distant or remote from the occipital lobe and in the absence of hemianopsia.

It is recommended that attention to these findings may help the electroencephalographer in lateralizing organic cerebral lesions.

6. Triketopyrimidine metabolism: I. A pilot study of phenobarbital medication. — Ralph Rossen, Walter L. Nelson, Robert P. Jeud and John R. Torghele, Hastings, Minn.

Twelve paired schizophrenics were selected for evaluation of triketopyrimidine (barbiturate) tolerance study. Quantitative barbiturate blood levels, chemical metabolic studies and psychiatric behavior were correlated with the electroencephalograms. None of the changes in blood studies or EEG's before, during and after administration of phenobarbital in this group significantly altered the electroencephalograms.

As a result of this work, we discussed two important issues:

(*a*) Should periodic blood levels be determined for individuals receiving triketopyrimidine derivatives for long periods of time ? That is a specific barbiturate tolerance test.

(*b*) Should these factors be taken into consideration as well as seizure discharge as criteria for administration for this group of drugs ?

7. EEG studies of choline deficient rabbits. — Jean Shephard and R. G. Black, Toronto, Ont.

The EEG's of 6 normal rabbits were compared with those of another 8 rabbits which had been receiving a choline deficient diet.

After procaine injection, Michele clip electrodes were fixed into the skin. Electrode placement, electrode resistance, machine gain and frequency response were standardized. Recordings of nose wobble, tremour, breathing, etc. were taken and the EKG recorded throughout. A record was kept of the apparent state of the rabbit and its surroundings (light, noise, presence of other people and animals, etc). Records were read visually. The rabbits on diet tended to be lethargic and drowsy, so their records were compared with that of a rabbit in natural sleep.

The normal rabbits showed ''alert'' activity at 5-7 c/sec., and irregular ''relaxed activity'' at 4-6 c/sec. with 12-16 c/sec. spindles. Four showed bursts of sharpish 6 c/sec. activity. Those on diet varied from apparently normal to a tendency towards slowing. Spindles remained unchanged. Four had runs of regular high voltage 3-4 c/sec. activity. These were not the 4 which seemed to be most effected by the diet, or which died first from the effect of the diet. All rabbits had little activity posteriorly, most activity anteriorly and a tendency towards more regularity in the more lateral electrodes. The runs of 3-4 c/sec. activity varied in location in the same rabbit.

The results suggest that there may be slow activity present in the EEG's of rabbit on choline deficient diet.

8. Time distortion in electroencephalograph amplifiers. — M. G. Saunders and R. M. Jell, Winnipeg, Man.

The capacitors used in EEG amplifiers produce phase distortion. This form of distortion can produce alteration of the time of appearance of components of compex wave forms and produce fallacious latencies of response to stimuli.

Whilst this form of distortion is probably of little significance in clinical electroencephalography it can be of considerable significance when measuring and interpreting stimulus-response times and when relating components of complex wave forms to one another.

9. Isopotential fixation position maps, relating eye-position and sets of potentials recorded from periorbital surface electrodes, for studies of direction of regard over the field of view. — Christine Kris, Cambridge, Mass.

An ''Isopotential Map'' is a graphic representation of potential difference equivalents of fixation positions.

A method of isopotential mapping of the periorbitally measured potential differences corresponding to all possible directions of regard has been developed to provide a means for registration of the course of changes in regard over the fixation field when the subject is allowed to look where he pleases or is asked to carry out a task.

The data from which the isopotential map is made is the set of recorded potentials corresponding to each of a controlled sequence of fixation positions, obtained by asking the subject, with head fixed, to look at each of a number of fixation targets having known angular positions with respect to the subject's orbits. This is facilitated by the use of the electrically controlled, hemispherical angulometer.

Since variations of the corneo-fundal polarization, and between potentials from different electrode pairs, occur as external and physiological conditions change, a given map can be used without correction by recalibration only as long as the magnitude of the accumulated variations remains below some predetermined level. The choice of this level depends upon the required precision of the eye-movement determinations. For relatively small potential variations, a correction through recalibration, and multiplication of potential values by a ''recalibration constant'' may suffice for continued validity of a given potential map. When real-time data analysis is carried out, the effects of external and internal milieu changes on oculo-motor performance during perception can be studied.

The uses of the technique for color-field perimetry, for determination of visual field defects, or performance on signal sequence or tracking tests, and of the type and frequency of spontaneous changes of regard onto different parts of the visual world will be discussed.

10. Summary - Electroencephalogram in narcolepsy. — E. B. Cahoon, Toronto, Ont.

All the 101 records containing sleep rhythms during overbreathing out of a total of 9300 records were examined, 61 patients had the diagnosis of narcolepsy, and 54 per cent of these had drowsiness during overbreathing. One record made during an attack of sleep paralysis, during which he was unaware of his surroundings and stopped overbreathing, contained sleep rhythms of 2 to 7/sec. and 17 to 25/sec. waves. The non-narcoleptic group suffered from mental illness in 30 per cent, head injury 17 per cent, infection 5 per cent, vascular accident 7 per cent and epilepsy 17 per cent. Three of these were toxic psychosis due to Sparine, Trilafon and Benzadrine respectively. It was considered that drowsiness during overbreathing was very suggestive of narcolepsy, as it occurred in 57 per cent of narcoleptic patients during overbreathing and only in 0.4 per cent of non-narcoleptic records. Dreams of teeth falling out occurred in 10 per cent of narcoleptic patients.

11. EEG, clinical and other findings in 500 selected and unselected prisoners. — B. K. Bagchi, W. S. Wille, Philip Bannan, L. Kelly and H. D. Calhoun, Ann Arbor, Mich.

This study comprises a selected group of 446 adult prisoners referred for EEG by psychiatrists and internists to help rule in or rule out ''organic'' conditions of CNS and 54 unselected prisoners without any specific reason.

Mild to marked abnormality including spike-wave were present in 38 per cent in the selected group (with or *without* clinical seizure) as against 30 per cent in unselected group and 3 per cent in 100 outside clinically normal control group. The variable of age did not make much difference. These findings agree in principle with those reported in the literature by others (Trans. Amer. Neurol. Ass., p. 87, 1942, Arch. Neurol. Psychiat. p. 38, 1944, J. Neurol. Psychiat. p. 47, 1952, but not with those reported in Amer. J. Psychiat. p. 294, 1945-46). In the first, second and last studies no temporal leads were used.

Not disregarding the fact that correlation is not necessarily causation and that legal reasons for incarceration not necessarily psychiatric reasons, we selected 40 variables (neurological, psychiatric, EEG rating 1 to 5, EEG temporal, non-temporal, or bioccipital focus, legal reasons for imprisonment) and correlated them against each other on an I.B.M. computor 650. A few significant correlations at 1 per cent level are given here: any type of seizure or seizure history and EEG rating; any seizure including ''temporal lobe'' seizure and temporal focus; headache and history of head injury; early behavior disorder and recidivism, aggressive behavior, stealing, mental retardation; crime of extreme violence and aggressive behavior; first degree murder, alcoholism, manslaughter, recidivism, sex crime and higher age group. Trends of association (not statistical significance) are found between bioccipital focus and early behavior disorder, manslaughter; temporal focus and murder. If detailed and accurate psychiatric, neurological and EEG observations are obtained making statistical treatment of data meaningful, some hitherto unsuspected parameters of criminality may be uncovered leading to social action on certain fronts.

12. The EEG in Jakob-Creutzfeldt's disease. — John Abbott, Boston, Mass.

Serial EEG's were recorded from two men with Jacob-Creutzfeldt's disease. The men were 58 and 59 years old. They were definitely ill for 5 and 8 months. One may have shown prodromal disabilities for a year. Their brains were examined *post mortem*. From each the first EEG was recorded at the beginning of hospitalization and the last in the last week

of illness. The EEG's showed regularly recurring diffuse, high-voltage sharp waves. These increased in prominence early in the illness and at this time occurred up to 21 times in 10 sec. and rose to around 350 μV. Their highest voltages were medial and either anterior or central in location. Their voltages and frequencies diminished in the course of illness: they sometimes occurred 3 times in 10 sec. in the last week of illness. Activity between these sharp waves or bursts underwent the following changes: normal frequencies were replaced by more and more theta and some delta frequencies; voltages of these slow frequencies dropped; finally (1 pt.) the record became almost flat between bursts. There was some evidence that (1) a loud noise could sometimes cause suppression of the bursts, (2) bursts and diffuse muscle jerks coincided in time, (3) bursts diminished or disappeared during convulsions, and (4) bursts occurred less frequently in sleep.

13. Autocorrelation and crosscorrelation studies of the EEG in man. — M. A. B. Brazier, L. S. King and R. S. Carpenter, Boston, Mass.

Among the applications of autocorrelation and crosscorrelation analysis which we, together with our colleagues in the Research Laboratory of Electronics at M.I.T., have been using in EEG studies are the following: studies of the phase relations of alpha waves to their neighbors in reference to the question of enduring pacing of the alpha rhythm, in contrast to those of unrelated bursts of alpha. In addition, studies were reported of the long-persisting oscillatory after-discharge following a flash stimulus in man. Experiments to determine whether these two oscillatory phenomena can be influenced to vary independently were reported. These included a study of changes in the alpha and after-discharge rhythms: (1) with varying thyroid hormone level in patients; (2) with altered epinephrine levels in normal subjects.

CZECHOSLOVAK ELECTROENCEPHALOGRAPHIC SECTION

Carlsbad, October 9, 1958

Secretary: Doc. Dr. IVAN LESNÝ,
Charles University, Neurological Clinic, EEG Laboratory, Prague 2, Kateřinská 30

1. EEG studies in tumours involving the mesodiencephalic region with special reference to the occurence of sleep rhythms. — M. Jindrová, B. Roth, J. Stein, M. Zuklínová, Prague.

The authors analyzed 141 tracings of 92 patients with tumours which infiltrated or compressed the mesodiencephalic region. In extracerebral tumours they found signs of pathological activity in 59 per cent, in the intracerebral ones in 86.3 per cent of the tracings. The EEG abnormality consisted in a generalized slow activity with a frontal maximum; episodes of hypersynchronic slow waves were frequent, especially following hyperventilation.

EEG signs corresponding to somnolence or to sleep were found in extracerebral tumours in 55.7 per cent, in intracerebral tumours in 33 per cent of all tracings. Sometimes these signs were accompanied by clinical symptoms of drowsiness or sleep, in other ones their occurence was purely infraclinical.

In the author's opinion the appearance of infraclinical signs of sleep rhythms has to be considered as one of the first symptoms of injury to the mesodiencephalic reticular activating system.

2. Further experience with accoustic stimulation of EEG using a constant tone with different frequencies. — I. Lesný, J. Odvárková, J. Stein, Prague.

EEG examination was performed in 230 patients mostly children. These records were activated by a constant tone with different frequencies. Seven frequencies were used: 1700 c/sec., 1400 c/sec., 1100 c/sec., 900 c/sec., 680 c/sec., 450 c/sec. and 200 c/sec. The patients were stimulated for 15 sec. The pauses between the stimulations were 30 sec. The changes of EEG following acoustic stimulation are various. The most frequent are: shift to the slow side, lowering of the voltage of all frequencies and epileptic discharges.

It appeared that the changes of bioelectric potentials following acoustic stimulation are much greater in the extreme tones — high and low — than in the middle ones. The lowering of voltage is mostly pronounced in high frequencies, the shift to the slow side in low frequencies. Electrical epileptic discharges followed acoustic stimulation in one half of cases having clinical seizures.

The sonogenic changes of the EEG are in children more considerable than in adults. In 6 children with severe developmental disorders of the brain the acoustic stimulation of various frequencies was followed by a constant fast activity 20 c/sec. in the midline (transverse) leads. This rhythm lasted for several seconds. We propose to call it ''epiphonic fast activity''.

3. The rolandic "arceau" rhythm as an electroencephalographic symptom of focal cerebral lesion. — L. Cígánek, Bratislava.

Six cases (focal epilepsy, head injury, brain tumor postoperatory state) are described with unilateral rolandic ''arceau'' rhythm in close proximity to the seat of the lesion.

4. A contribution to the problem of rolandic "arceau" rhythm. — L. Cígánek, Bratislava.

One case with a prominent beta rhythm 27-30 c/sec. in central regions bilaterally was described. In both central parasagittal regions the beta rhythm was transformed from time to time in a typical rolandic ''arceau'' rhythm 9-10 c/sec. Intermediate shapes of waves between both sorts of activity were observed. Both the beta and the rolandic rhythm were resistant to the opening of the eyes but reacted when blocked by the movements of the extremities, predominantly on the contralateral side. The movement of the foot exerted its influence more upon the activity in the sagittal line, the movement of the hand was more

effective in the parasagittal regions. This findings support the conclusions of Gastaut, Terzian and Gastaut about the character of the rolandic (''arceau'') rhythm and about its relation to the central beta rhythm.

A brief review of other activities with archlike shaped waves is given and a hypothesis is proposed about a general lawfulness of electrogenesis in the brain shown by involving these activities.

5. Photostimulation in patients with expansive basal brain and posterior fossa lesions. — J. Stein and B. Drechsler, Prague.

The authors have examined EEG employing photostimulation in 40 patients, of these (*a*) 18 with posterior fossa tumours, and (*b*) 22 with ''brain base tumours'' (i.e. meningiomas of the sulcus olfactorius, tuberculum sellae, ala parva, craniopharyngiomas and other tumours of the same location). In most cases they have further employed provocation by means of intravenous thiopental injection test. They have arrived at the following conclusions:

1. Evoked potentials are very poor in brain base tumours patients, whereas the photosensibility is very good or even normal in case of posterior fossa lesion patients.

2. On the other hand the response to the intravenous thiopental injection test is considerable with brain base tumours patients, while with posterior fossa tumours it is very slight.

3. The authors find the reason for subnormal photosensibility in case of suprasellar tumours in the affection of the neighbourhood of ventricle III (thalamus, oral parts of the brain stem) by pressure or by direct infiltration of an expansive process.

4. Asymmetries in the response to photostimulation appear occasionally in cases of posterior fossa tumours: the photosensibility over the opposite brain hemisphere is reduced rather more frequently, but the difference as compared with cases of worse photosensibility over the homolateral brain hemisphere is rather slight (the ratio being 3:2).

5. The authors conclude that the photostimulation results are of practical significance in the differential diagnosis of brain base and posterior fossa expansive lesions.

6. Tetany and Epilepsy. — B. Roth and O. Nevsímal, Prague.

The authors found in 44 cases of hypocalcemic tetany 15 patients with epileptic seizures of different kinds. They also observed other patients with generalized tetanic spasms with or without loss of consciousness. Seven patients showed psychotic symptoms, 18 neurotic signs and in one case the authors found the symptomatology indicating the presence of a pseudotumour. The EEG changes were pronounced in all untreated cases with or without cerebral symptoms. They consisted in a generalized slow activity, more frequently of the theta band. Overbreathing had a very strongly activating effect. Epileptic features have been found in the recordings of patients with epileptic fits and in some of the other cases also. Antitetanic treatment was followed by normalization of both the clinical and EEG findings. In the authors' opinion all central nervous symptoms, the EEG changes included, are caused by hypocalcemia, which raises the excitability of the central nervous system and produces cerebral oedema.

The authors discuss further the possibility of the occurrence of epileptic seizures in normocalcemic tetany quoted by Klotz. On the basis of a study of 89 personally observed cases of normocalcemic tetany they conclude that this relation is as yet not satisfactorily demonstrated.

7. Reflex reactiveness of neuromuscular system in spastic conditions. — B. Drechsler, V. Janda, J. Pfeifer and V. Skorpil, Prague.

The authors examined 25 patients with a remarkable syndrome of spasticity of hemispheral, brain stem and spinal origin. The electromyographic examination was based on the works of Magladery and col., Paillard, Strupler. Using electrical nerve stimulation with increasing intensity the authors correlated especially the tendon reflex, H reflex and the direct motor response in the same muscle. They reached the following conclusions: the latency of these reflexes is unchanged; the tendon reflex response is often desynchronized and increased, response for the H and M reflex has often an increased threshold of stimulation and there is often a reversed succession of beginning of the both appearances. Antidromic inhibition of H reflex is often insufficient and sometimes even absent. The spinal localization of the lesion seems to cause the reversion of normal succession of the reflexes more than in the others localizations. This objective examination technique is of value in the clinical praxis.

THE DANISH EEG SOCIETY

Institute of Neurophysiology, Copenhagen

November 26, 1957

Secretary: W. TROJABORG

The EEG-Laboratory of the University Clinic of Copenhagen, Denmark

1. EEG activation with Megimide. — J. Ellebjerg and P. Jacobsen, Filadelfia Colony.

Megimide was used in order to obtain another method of EEG provocation besides Metrazol. With Megimide provocation — 14-18 ml. (5 mg/ml.) in varying dosage (at last initial 4 ml. + 2 ml/min. × 5) — in 39 normal members no EEG alterations appeared in 24, more or less pronounced diffuse dysrhythmia in 11 and paroxysms in 4 cases — in one spike and wave after 4 ml., in another after 18 ml. Most of the subjects had no symptoms at all, two reported dizziness, anxiety and nausea.

Megimide provocation was carried out in 80 patients and in 64 of these with Metrazol as well —

max. 3.5 ml. 16 per cent sol. adjusted to weight and at ½ min. intervals. Twelve patients had certain epilepsy, 52 some attacks of very varying kinds, all of them hospitalized to diagnose or eliminate epilepsy. Two patients subjected to provocation in order to activate focal abnormalities had their usual anti-epileptic drugs, in other patients anti-epileptic drugs were stopped at least 6 days before provocation. At least 5 days elapsed between the 2 provocations. The same dosage of Megimide was used as in normal persons.

The EEG alterations were often qualitatively the same but quantitatively more pronounced by Metrazol than by Megimide. The results in patients with certain epilepsy suggest that some more than 14 ml. correspond with 3.5 ml. Metrazol. The subjective symptoms were more pronounced with Metrazol than with Megimide, whether EEG alterations were found or not. With Megimide no clinical seizure appeared, with Metrazol a grand mal in one patient.

Our preliminary results need further investigations before our trials can indicate advantages of Megimide as EEG activator. (Later results will be published in *Acta Neurol. Psychiat. Scand.*)

2. EEG in strangulation and heart stop. — N. Bokonjic, Copenhagen.

The study deals with a correlation between clinical and EEG findings in 21 patients with anoxia cerebri. Fourteen patients had attempted suicide by hanging, in 2 the strangulation was accidental and in 5 heart stop occurred during operation.

The patients were grouped in three groups according to the duration of the unconsciousness.

The first group contained 13 patients (hanging) who all had a period of unconsciousness from a few minutes to 14 hours. After the return of consciousness the patients were confused and the EEG was characterized by a mixture of 5-7/sec. activity and activity of more than 14/sec. both with an amplitude of 40-100 V. The patients in this group all showed complete restitution after 1-30 days both clinically and electroencephalographically. The longer the duration of unconsciousness, the longer the restitution time. The degree of EEG abnormality was correlated to the clinical state during the restitution.

The second group contained 3 patients (heart stop) in whom the period of unconsciousness was from 24 to 48 hours. One of the patients had a dementia when the restitution time was over, the two others, even after complete clinical recovery, showed paroxysmal changes in the EEG (spikes and sharp-waves). During the time to partial recovery EEG changes were like those found in group one, but the slowing was more severe (3-6/sec.). In one case the EEG changes were focal.

The third group contained 5 patients (2 strangulation, 1 hanging, 2 heart stop) in whom the unconsciousness had a duration of more than 9 days. Three of them died, in two patients chronic severe disablement remained. The EEG from this group was characterized by initial absence of activity followed by appearance of assymetrical 3-5/sec. in the frontal and temporal regions. In two cases the findings were focal.

In the second and third groups the recovery of the electrical cortical activity was parallel to clinical recovery, especially in the initial phase, but the final results were not correlated in that EEG abnormalities persisted in spite of complete clinical recovery in two cases and the EEG was normalized but lack or complete recovery in two cases.

3. On the patho-physiology of the 3 per second spike and wave epilepsy. — D. H. Ingvar, Lund, Sweden.

The cause of 3 per sec. spike and wave epilepsy is still unknown. Clinical and experimental evidence has been brought forward for the existence of a focal lesion in the upper midbrain in this disease. By its medial placement, in structure with access to both hemispheres such a focus could be able to interfere with cortical electrical activity in a "bilateral synchronous" fashion. Recent experimental evidence shows, however, that it is not possible to mimic the typical 3 per sec. spike and wave pattern in animals by electrical or local chemical stimulation in the upper midbrain. Clinical observations with depth recording have not either convincingly demonstrated a primary participation of thalamic or subcortical structures during 3 per sec. spike and wave seizures. The author has recently carried out animal experiments in order to study the cortical circulation and EEG during Metrazol induced epileptic discharges. Such cortical discharges, when elicited slowly, may show a transient stage of 3 per sec. spike and wave activity. This form of activity is probably related to a failure of local cortical circulatory homeostasis when the excitability is raised to abnormal levels by Metrazol.

4. Positive findings with nasopharyngeal leads in psychomotor epilepsy with vegetative symptoms. — W. Trojaborg, Copenhagen.

A 36 year old man with grand mal and psychomotor epilepsy since the age of 21 with negative findings by pneumography and clinical neurological examination.

During the EEG examination the patient had repeated attacks of impaired consciousness accompanied by flushing, mastication, grunting, sligth increase in pulse and blood pressure followed by incoordinated movements and without specific changes in the EEG recorded with scalp electrodes.

Leading off with nasopharyngeal electrodes just after a seizure bursts of fast activity 18-24 per sec. 75 μV. appeared localized to the right nasophyryngeal electrode. These findings were reproduced repeatedly and were observed always immediately after psychomotor attacks.

PRINTED IN CANADA

BOOK REVIEWS

Edited by CHARLES E. HENRY

THE PHYSIOLOGY OF THE NERVOUS SYSTEM

E. GEOFFREY WALSH

London, Longmans, Green & Co. 1957. Pp. xvi + 563 + 6 plates. 50 shillings.

This book carries the same title as Dr. Fulton's well-known textbook but it contains startlingly different material. In fact, there is scarcely any overlap. The reason is that Dr. Walsh's book is not a textbook of the physiology of the nervous system but a book of applied neurophysiology — applied, that is, to experimental psychology and to clinical neurology. Dr. Walsh makes this clear in his introductory paragraph. Our need for texts that fill the gap between fields is very great. He is to be congratulated on entering it.

Dr. Walsh builds a welcome bridge between neurophysiology and neurology, but his reader needs to have considerable knowledge of the territory on both banks before he can appreciate and assess this bridge. He will not learn either his physiology or his neurology from this book (the nerve impulse gets only a cursory explanation, synaptic transmission a few pages), but he will find just enough to remind him of these things. (Lloyd's chapters in Howell's *Textbook of Physiology* are still the outstanding source in which the student can find this information.)

As in all books, some chapters are more successful than others. Those on posture and on the cerebellum are extremely interestingly worked out, and although again the explanations of the basic neurophysiological events are skimpy these two chapters are the most successful. (Germandt's work on the vestibular system, for example, is given mention in two lines, Moruzzi's on the cerebellum two sentences.)

The chapter on the visual system written in the context of experimental psychology is also exceptionally well done and brings together a great deal of interesting material from many sources, comprehensively and skillfully interwoven so as to relate to conditions of disordered perception.

Readers of this journal will perhaps be especially interested in knowing what they may learn about electroencephalography from this book. They will find the subject bundled into the same chapter with strychnine neurography, olfaction, phrenology, Lashley's ideas of equipotential, conditioned reflexes, facial paralysis, temporal aspects of behavior and consciousness. Dr. Walsh has something interesting to say on each item in this strange packaging. Where else would one find a comment by Wiener on the automatic computation of differential equations in the same chapter as quotations from the usual accounts that are written about Miss Helen Keller ?

In his treatment of electroencephalography Dr. Walsh relies very heavily on the work of the 1930's. His account of alpha blocking ignores the elucidation of this phenomenon that stems from the work of Moruzzi and Magoun (this classic paper is given three lines). He gives a misleading figure of the fields of current flow in the head that depicts "the origin of the alpha rhythm" as lying in a region which in his diagram would be just posterior to the Rolandic fissure. The caption implies that this illustration is derived from Adrian and Matthews, but these writers should be exonerated.

Although Dr. Walsh clearly knows too much to subscribe to the proposal that EEG waves are the envelopes of spikes from discharging cells or axons he nevertheless reproduces two illustrations (from the 1930's) based on this postulate and gives no space to elaborating the hypotheses that have been suggested as alternatives. Even in the thirties Gerard was saying: "I do not believe that most of the large, regular electrical potentials that one observes in neural masses prove the passage of nerve impulses — and am inclined to attribute especially the slow potentials largely to electrical variations within the cells themselves, which are not transmitted along axons and which modify the potential activity of a mass of nerve cells rather than indicate the discharge of impulses from them". The mass of experimental data that has come to the support of this view in the last 20 years is given no place in this book.

The recruiting systems of the diencephalon and the arousal systems of the mesencephalon are very inadequately dealt with, and the caption to the reproduction of Bremer's famous illustration suggests either that the author has not fully understood Professor Bremer's classic contributions or that he is not familiar with the cortical potentials of the cat (in contrast to man).

Dr. Walsh forgets his comparative anatomy when he labels Dempsey and Morison's well-known illustration of the cat's brain as that of a dog, and forgets Cajal (and many others) when he says of Starzl, Taylor and Magoun's schema of afferent collaterals to the reticular formation (a block diagram that depicts no detail) "the anatomy — is not defined

with the exactitude that this figure might lead one to suppose''. Less important slips are that we are told that Berger was an Austrian (he was German) and repeatedly Herbert Spencer is given an aura of a Faerie Queene by being spelled with an ''s''. But the latter are trivial, minor slips that do not mar the book which has considerable value as a source book because it contains an extensive list of references in clinical neurophysiology that have not been brought together before in quite this way.

Possibly the inappropriate titling of this book was a publisher's quirk (as probably also was the unfortunate way of numbering the illustrations) but perhaps this misnomer will not detract from its circulation. After all, one of the most famous books in our field, dealing principally with the neurophysiology of the decerebrate animal below the transection, has flourished under the misnomer of the *Integrative Action of the Nervous System.*

Mary A. B. Brazier

A MANUAL FOR EEG TECHNICIANS

RHODA FEINSTEIN MILNARICH

Little Brown & Co., Boston, 1958, 222 pp., $5.50

This book, a welcome addition to the EEG technician's library, fills a great need since it is only the second book so far published specifically for technicians, who as a class do not have adequate facilities for training. Very few institutions offer formal courses, and electroencephalographers, the usual source of training, have little time to organize competent inservice instruction. As a result of their inadequate preparation, many technicians work in a somewhat robot manner, according to the electroencephalographer's general instructions. And yet the skill in making the tracing is as important as the knowledge required for its evaluation. Books written especially for electroencephalographers, however, are too advanced for technicians without formal training. For them this manual bridges a real gap in the technical literature.

In preparing the book, the author visited many laboratories to obtain a wide view point and suggestions from both electroencephalographers and technicians. The foreword, by Dr. Robert S. Schwab, Director of the Brain Wave Laboratory, Massachusetts General Hospital, points out the need of a basic book for technicians, whose important role he emphasizes. The last chapter is written by Frances Potts, a technician in this laboratory.

The first chapter, on the role of the electroencephalographer, points out his responsibility both for the laboratory and to the technician. A list of important journals containing EEG material is appended to the chapter.

In the second chapter the author defines a few basic electronic terms and explains the basic principles of the electronic amplifiers, tubes, resistors and condensors. The reviewer would prefer a more detailed explanation, however, of push-pull amplification, a type of amplification very generally used; and of the different types of tubes, for example, how rectification takes place in the rectifier tubes and the principles of operation of the oscillograph. The author in explaining filter controls (p. 19) should note that changes occur in both the value of the resistance and in the value of the condensor when a change is made in the time constant of the circuit.

Chapter III, an introduction to the complexities of the electroencephalogram, first discusses the rudiments of brain structure. Every technician should have some basic knowledge of cerebral anatomy. Many of the terms used to describe EEG activity are well explained, as is the type of activity considered normal or abnormal for different age groups. The author also emphasizes the major factors involved in the interpretation of the electroencephalogram, and their correlation with the patient's clinical history, symptoms and physical examination. She does not discuss the anatomic structure and location of the different sections of the brain and their functions, factors extremely important in the localization of brain lesions. A diagram of the different areas which pertain to speech, vision, motor movements, etc., would be very helpful.

Next comes a chapter on the relationship of the technician to the patient — the importance of understanding the patient's emotional and physical state and some of the reasons for referral. The technician is advised how to answer some of the most common questions. Many helpful hints are given on how to obtain good recordings and maximum cooperation from children and from patients with organic disease and mental illness. Here the author's long experience is well demonstrated.

In chapter V the author describes the usual types of electrodes and explains the construction, including the coating of a silver electrode with silver chloride, with helpful suggestions for good application of the different types. A statement as to the advantages and disadvantages of the different types might be of value to the new technician. The author's emphasis on keeping the electrode contact-resistance below 10,000 ohms is indeed the ideal, but not always pos-

sible, particularly when electrode paste is not used.

Perhaps the most important chapter for the beginner is the sixth, ''Artifacts'', since the prompt identification of all artifacts is necessary for a proper technique. This chapter, an excellent guide, has many fine illustrations. The common reasons for artifacts are explained, as well as the problem of how to check electrode artifact and the result of nonsymmetrical electrode placements. Artifacts caused by outside electrical interference, defects in the apparatus, movement and physiological sources, their causes and best methods of dealing with them, are included, but not that of shielding against electromagnetic and electrostatic fields, on the ground that it is beyond the scope of this manual. Actually this very important problem faces all new technicians and therefore should be discussed. In the section on defects in the apparatus one could explain that the instrument can be eliminated as a source of artifact if it calibrates correctly, and further that battery noise is often a source of artifact common to all channels of the instrument.

Pictures of nearly every type of electroencephalograph are shown in chapter VII, ''Recording on the Electroencephalograph''. The location and purpose of many of the switches and controls are given, with two excellent analogies to illustrate the use of gain controls. Some of the duties of the technician during the recording procedure and the types and purpose of some of the activation procedures are discussed, with excellent illustrations on the effect of activation on the EEG. In the discussion of recording procedures, scalp-to-scalp and common-referrence recordings are briefly noted; but the advantages and disadvantages of the two techniques are not discussed, nor are the electrode placements and runs used in many of the laboratories. A thorough understanding of recording techniques is necessary if the technician is to have freedom in selecting proper runs for each individual case, as is mentioned (p. 117). Although a phase reversal and artificial phase reversal are well illustrated, what takes place in the brain when a true phase reversal occurs is not explained.

Many of the physiologic and pharmacologic factors affecting the electroencephalogram are discussed in chapter VIII. The awake electroencephalogram of a normal child and the different phases of sleep in the normal child and adult are nicely described, as are the changes that take place in the electroencephalogram for such factors as blood sugar level, drugs, electroconvulsive therapy and the menstrual cycle.

The first portion of chapter IX, ''Seizures'', has several excellent illustrations of the different types of EEG's recorded on patients with petit mal, grand mal and other types of seizures. Occasionally a patient may have a seizure during the recording. Important points to be reported on the seizure and the duties and conduct of the technician while recording are discussed. The emergency treatment to be rendered by the technician in the case of a grand mal seizure is briefly noted. A good description of the electroencephalogram and the seizure is given for many of the different types of convulsive disorder. There is also an excellent comparative figure of a tracing on a patient with hysterical seizures (p. 163).

Every technician has some administrative duties to perform. The tenth chapter thoroughly covers such duties as the technician's report, the electroencephalographer's report, the obtaining of diagnostic information, filing and scheduling. A practical outline for daily routine is suggested.

The last chapter concerns recording during special procedures such as at the bedside or in surgery and gives the necessary equipment and preparation; including such important factors as grounding, oxygen, power source and conduct in the operating room. The chapter is brief but well written.

This elementary book contains little new information for the experienced technician and, as already noted, many chapters lack detailed information. A chapter on the maintenance of the instrument might well be included. But the book is a well organized, well written one for the student technician.

G. Lawrence Mowery, M.D.

THE VERTEBRATE VISUAL SYSTEM

(Its origin, structure, and function and its manifestations in disease with an analysis of its role in the life of animals and in the origin of man.)

STEPHEN POLYAK

The University of Chicago Press, Chicago, Ill., 1957, 1390 pp. $45.00

This book, like its forerunner, The Retina, published in 1941 by The University of Chicago Press, originated in the desire to understand better the anatomical structures underlying vision. During the last years of his life, the author was in ill health with the constant worry that he would not be able to complete the manuscript. His long-time friend, colleague and confidant, Heinrich Klüver, promised to complete the work, should he leave it unfinished. After Polyak's death, Prof. Klüver devoted two years of his scientific life to the job of finishing Polyak's monumental work.

The volume consists of 4 parts:

The *first part* deals with the *history* of investigations of the structure and function of the eye, as well as of the visual pathways and centers of the brain. It presents the development of our knowledge of the bodily mechanisms underlying vision from the earliest efforts to the following ages and to our own time. This section is an impressive memorial to the many workers who gave us our present knowledge. Historical investigation reveals both the temporal sequence of the discoveries and the ideological motivation for subsequent investigations.

The *second part* deals with *anatomy and histology* of the retina, as well as the visual pathways and centers of the brain, principally in man, apes, and monkeys.

In the *third part* the pathology of the retina and pathways or centers of the brain is exposed, with special reference to the various visual field defects. This part helps to understand the pathology of vision and adds to our knowledge of the organization of the visual apparatus.

In the *fourth part,* Polyak discusses the *origin, development, comparative anatomy, physiology* and *biology* of the vertebrate organs of sight. He shows how the eye may have initiated the formation of the brain and how vision in turn has given an evolutionary impetus to the rise of the primates, eventually culminating in the advent of man.

The work consists of 1055 pages of text, abundantly illustrated (546 figures, many of them in colors), and 300 pages of bibliography, containing approximately 10,000 references. It is a compendium of our present knowledge on vision and on the relations between eye and brain. The book is written not only for advanced investigators or ophthalmologists, but also for students in neuroanatomy, neurophysiology, clinical neurology, ophthalmology and related fields. It shows in which directions further investigations should be undertaken for a better understanding of the material basis of vision and brain functions. We agree with the author when he suggests that the analysis of the minute structures of the visual centers and of the synaptical relationships of neurons is a particularly important research topic.

This volume provides valuable information to neurophysiologists on descriptive and comparative anatomy of both visual pathways and brain centers. Although it does not contain many electrophysiological data, it is of much use to readers interested in problems of the organization of the nervous system. For research work on vision and brain functions in various species the book is a unique source of information. Generations of investigators will appreciate the tremendous work that Polyak and his friend Klüver achieved, with the purpose of facilitating their own research work.

MARCEL MONNIER

MORPHOLOGIE UND PHYSIOLOGIE DES NERVENSYSTEMS

PAUL GLEES

Georg Thieme, Verlag, Stuttgart, 1957, 445 pp. $13.50

The title of this volume implies that it is a textbook dealing with the correlation of structure and function of the nervous system. However, as indicated in the introduction the author has set himself the task of presenting the most prominent results of experimental neurology as they have evolved from laboratory research, particularly in Neurophysiology, during the past 10 years. Thus we are curious to determine whether this volume is to be a modern textbook or a comprehensive progress report. Unfortunately, this ambiguity does not resolve itself in the many chapters that follow. In our opinion, the book offers far more than a review (especially because of its beautiful illustrations) and yet it does not include the lucid and logically organized treatment of basic information required for a textbook. When considering it essentially as a progress report — as the present reviewer prefers to do — many of the criticisms which for a textbook would seem inevitable can be dismissed and the following discussion can be restricted to the question: Is the review up to date, comprehensive and critical? To digest and evaluate data from the world literature in this particular area of research is a formidable task and in our opinion the correlation of chemical, electrical, microscopical and psychological information by any one individual can hardly be done to the satisfaction of the specialists. Certainly, among the few candidates who can qualify for such a review, Paul Glees comes to mind immediately, having worked in both anatomical and physiological laboratories in Germany, Holland and England and having had the privilege of world wide laboratory tours and of personal and on-the-spot exchanges with practically all of the world's celebrities in brain research. The result of the author's efforts is an up-to-date, comprehensive but unfinished and rather personal outlook on developments in this field.

A glance through the bibliography convinces the reader that the quotations are internationally com-

prehensive and up-to-date (the book is dated 1957 and contains references to articles of 1958 !). The admiration for this unique accomplishment on the part of both writer and publisher is somewhat attenuated by the fact that the book is also unique in the number of errors, i.e., misprints, lapses of style and grammar, mispelling of author's names (we counted 20), erroneous cross references to pages and illustrations, and a most peculiar inconsistency in the spelling of Latin and Greek terms and their Teutonic derivatives: (For example: cervical, cervikal and zervikal. Why not zerwikal ?).

The material is presented in 18 chapters, the first six of which deal with methodology, biochemical aspects, receptor function, nerve conduction, synaptic transmission and spinal reflexes. The three following sections are devoted to somatic sensory and motor functions of thalamus and cortex. Such important items as two-point-discrimination and integration of space and time factors are discussed rather sketchily, and figure 69 offers a supposedly simple explanation of the recovery of tactile sensation after the corresponding somatotopic area of the postcentral gyrus has been damaged. An analogous scheme explains the mechanisms of recovery of motor function with lesions of the precentral motor cortex. Unfortunately, the existence of multiple representation areas receives little or no attention in this regard. Rather, the author resorts to thalamo-cortical ''detour'' pathways and a plurisegmental dispersion of corticospinal connections (both of which are still wanting for solid documentation). The next chapters are concerned with cerebellum, basal ganglia and hypothalamus. Surprisingly, enlightment on such current topics as obesity, appetite, thirst and emotional disorders are sought in vain. The chapters on reticular formation, electrical activity of the cerebral cortex, auditory and visual systems and a general round-up on cortical areas conclude the volume. It can be predicted that the inadequacy of the chapter on the autonomic nervous system (5 pages) will be disturbing to some and the lack of a separate review of the rapidly accumulating information on the morphology and physiology of the limbic system to other readers. The treatment of olfactory pathways and functions boils down to the statement that the hippocampus may not have much to do with them. On the other hand, the rare mentioning of vestibular and gustatory functions seems excusable since they do not happen to be popular in our time.

The attitude of Glees toward research in general and toward individual contributions (not excluding his own) is one of kind optimism and conciliation. This and his talents for synthesis afford fluent and pleasant reading of his text. On the other hand, it may occasionally leave the soberly minded reader with the uneasy feeling that golden bridges between function and form are being constructed which may not bear the weight of critical tests. In instances, where more objective reviewers would criticize an author for lack of evidence or use of inadequate technique, Glees merely mentions his claims without critical examination, to mention only the rather soft treatment of Kornmüller's anti-neuron theory of the synapse (p. 105) or the noncommittal discussion of controversial material concerning hypothalamo-hypophysial relations put forward by the Spatz school (pp. 265-267).

In its present form the book contains sufficient information on methods, results and ideas to make a German reader curious about such matters. Many an issue he will find clarified in Richard Jung's ''Allgemeine Neurophysiologie'' (cf. review in this Journal, Vol. 7, p. 670, 1955).

KONRAD AKERT, M.D.

FUNDAMENTALS OF CLINICAL NEUROPHYSIOLOGY

PAUL O. CHATFIELD
Charles C. Thomas, Springfield, Illinois, 1957, 392 pp. $8.50

In this volume, the author attempts ''to present a one-man, integrated view of the better-established facts of neurophysiology'', using the material gathered for the first year physiology course at Harvard Medical School.

Despite its title, the book is not clinically oriented. There is emphasis on axonology, electrophysiology of the spinal cord and the nervous control of respiration, but the portions of the brain above the tentorium are treated in rather cursory fashion. There are notable omissions, with no consideration of such aspects as cerebral blood supply and vascular mechanisms, the cerebro-spinal fluid, brain metabolism, pathologic reflex phenomena in man, and anesthesia.

The information presented is well documented with references to the earlier literature, but the concentration is on data, rather than on concepts.

JEROME K. MERLIS, M.D.

PRINTED IN CANADA

AUTONOMIC IMBALANCE AND THE HYPOTHALAMUS

Implications for Physiology, Medicine, Psychology and Neuropsychiatry

ERNST GELLHORN

University of Minnesota Press, Minneapolis, 1957. 300 pp. $8.50

The author attributes the origin of the experiments described in this monograph to the clinical observations made by Funkenstein, Greenblatt and Solomon with their test of autonomic balance. These workers showed that there were differences between neuropsychiatric patients and controls in the intensity of the blood pressure fall induced by mecholyl; they also demonstrated that the hypotensive effect of mecholyl changed with change in the mental condition of the patient. In view of Gellhorn's earlier studies on the relation between the diencephalon and psychic disorders, Funkenstein's results suggested to him the possibility of measuring the excitability of the hypothalamus in the intact organism through autonomic tests. The problem was attacked on a broad basis, with the aim of proving the validity of the idea, applying the underlying principle to the parasympathetic system and obtaining further clinical data on psychiatric patients and normals. In addition, he found it necessary to carry out an experimental analysis of autonomic imbalance and its ramifications, including hypothalamic cortical relations, somato-autonomic integration and homeostasis.

The book is organized into two parts and a summary chapter. The first part contains eight chapters in over 200 pages and deals with experimental investigations; the second part contains five chapters in 44 pages and deals with a review of the results and their clinical application. As the bulk of the volume consists of a compressed account of numerous experiments (there are 101 illustrations, most of them physiological records, 70 not previously published), the author was confronted with a difficult task of exposition. His success in this undertaking must be regarded as qualified, as he himself recognizes by advising readers who are not well acquainted with neurophysiological research to substitute summary accounts in later chapters for some of the earlier experimental chapters. This is good advice, and the reviewer would add that even the more experienced reader might find it worthwhile to go over the Summary and Conclusions chapter before reading the rest of the book.

In most of the experiments the blood pressure, the heart rate, and the contraction of the normal and denervated nictitating membrane were used as indicators of autonomic reactivity, with the curarized cat as the subject. The laws governing interaction of two stimuli acting on either the sympathetic or parasympathetic nervous system were then investigated under a variety of conditions. Several principles were thereby demonstrated which seem of fundamental importance, insofar as they extend to the autonomic nervous system concepts which have long been accepted for the somatic nervous system. For example, the law of reciprocal innervation seems applicable in the sense that sympathetically acting stimuli excite the sympathetic division and inhibit the parasympathetic division, or vice versa; furthermore this law seems also to hold in induced states of autonomic imbalance and at the hypothalamic level. Spatial and temporal summation are demonstrated for both divisions. The laws of summation form the basis for Gellhorn's concept of "reflex tuning" in the autonomic nervous system. Tuning occurs when the autonomic balance in the organism (in part or as a whole) is shifted to either the sympathetic or parasympathetic systems; this will lead respectively to a greater response from given sympathetic or parasympathetic stimuli. Such shifts in balance can be accomplished by lowering the blood pressure with acetylcholine, mecholyl or histamine, or by raising it with noradrenaline. The consequent changes in the baroreceptor reflexes (the importance of which is demonstrated by experiments involving sino-aortic denervation) elicit a shift to the sympathetic side in the hypotensive tests and to the parasympathetic side in the noradrenaline experiment. Sympathetic discharges are consequently increased in a state of sympathetic tuning, and a sympathetically acting test stimulus becomes more effective than under control conditions, a result interpreted as the summation of the effect of the test stimulus with the hypothalamic discharge which is increased in sympathetic tuning.

It is possible to mention only a few of the many other observations and ideas with important implications contained in the experimental section. The concept of neurogenic-adrenomedullary (N/A) quotient is used to designate the relative degree of participation of neurogenic and hormonal components in the sympathetico-adrenal discharge. These are shown to influence the reactivity of the autonomic nervous system in opposite manners, sympathetic responsiveness to direct and reflex stimulation being increased during a neurogenic discharge and decreased during marked adrenomedullary secretion. The importance

of proprioceptive impulses for maintaining the excitability of the posterior hypothalamus is documented. Evidence is adduced for tonic sympathetic and parasympathetic function mediated through the hypothalamus. The hypothalamus is shown to influence the excitability of the cortex and to have its own excitability influenced by the cortex, through so-called hypothalamic-cortical and cortico-hypothalamic discharges.

To this reviewer few serious criticisms may be directed at the experimental part of this book. One may question the validity of equating frequency shifts in electrical recordings with excitation, a shift to fast frequencies being regarded as evidence of increased excitation. However, it seems to be common practice nowadays to generalize this electrical correlate of behavioral arousal. The advisability of using the term ''recruiting response'' to indicate the elicitation of cortical spindles, similar to those seen in sleep, by stimulating thalamic or caudate nuclei may also be questioned. These are relatively minor quibbles. On the other hand, one may ask to what extent the author has been able to fulfill the applied aims indicated in the title of the book, and particularly with respect to neuropsychiatry, since the inspiration for the work is attributed to a clinical neuropsychiatric observation. This is admittedly a harsh standard, as the work could easily stand on its own without such applications, but it is one chosen by the author.

The results of mecholyl and noradrenaline tests on neuropsychiatric patients and ''normals'' are presented in one section. They show that autonomic reactivity, as determined by these tests, decreases with increasing age. Differences between patient and control groups on the mecholyl test were far from spectacular, the proportion of ''normal'' values being from 25 to 39 per cent lower in the patients groups at different ages. Comparisons between patients classed as schizophrenic and psychopathic personalities yielded even smaller differences, and the patient control differences with the noradrenaline test were apparently not significant. Consequently, although the material in this book contributes a great deal toward understanding the physiological significance of these autonomic tests, it does little to support the premise that such tests are to be taken as indicators of high relevance for the pathophysiology of neuropsychiatric disorder. Gellhorn's suggestion that psychiatric therapy be directed toward restitution of the normal sympathetic-hypothalamic reactivity cannot be disputed for those cases where such reactivity is deviant. However, there seem to be many patients with normal autonomic test findings, and one may have serious doubts about the extent to which restoration of normal hypothalamic reactivity would constitute a reversal of truly relevant pathophysiological processes.

Gellhorn's own data dealing with other autonomic indicators, such as the contraction of bladder and gut, lead him to conclude that ''in one organ a state of parasympathetic excitation may exist and in other organs a state of sympathetic excitation as a result of the reflex or hypothalamic activation of the autonomic system'' (p. 155). It would thus not seem logical to expect that any test employing one or two physiological responses, such as blood pressure or pulse rate, as indicators would be able to give more than a partial picture of autonomic reactivity. If the considerable overlap between clinical groups reflects this limitation of the tests, additional tests may provide greater differentiation and so support the thesis that autonomic imbalance plays a key role in the pathogenesis of psychiatric disorder. If, on the other hand, the degree of differentiation is not appreciably increased, this thesis may be questioned. This is obviously a most fascinating and promising area for future investigation, but it is important to realize that the issue is far from settled.

This monograph deserves a place on the bookshelf of all physiologists and of those workers in the psychological and medical sciences who would like to be able to go beyond vague statements about ''physiological factors'' when they speak about feelings and emotions. Although it provides little in the way of definitive answers, it may represent an important step toward arriving at some.

C. SHAGASS, M.D.

PRINTED IN CANADA

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The Colloquium and its publication have been made possible with the generous support of The Acadamy of Sciences of the USSR Moscow.

ERRATA

In the Society Proceedings section of the August 1958 issue, the last paragraph on page 576 should read: ''A significant but low correlation was found between performance on the Graham-Kendall test of memory for designs and basic EEG frequency in a group of 58 elderly neuropsychiatric patients, r=—.33. Correlations of —.47 and +.28 were computed between age vs. EEG frequency and age vs. Graham-Kendall scores respectively.''

In the November 1958 issue, table II, page 625, the columns headings should be labeled: *Mdn. %-Delta, Mdn. %-Alpha, Mdn. %-Beta.*

In the November 1958 issue, on page 643, table VIII, footnote 2 ''hematomas'' should read ''hamartomas''.

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FOR ELECTROENCEPHALOGRAPHY AND CLINICAL
NEUROPHYSIOLOGY, Inc.

PARIS, 1949

Chief Editorial Office, 3801 UNIVERSITY ST. MONTREAL, CANADA

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